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INTERNAL MEDICINE

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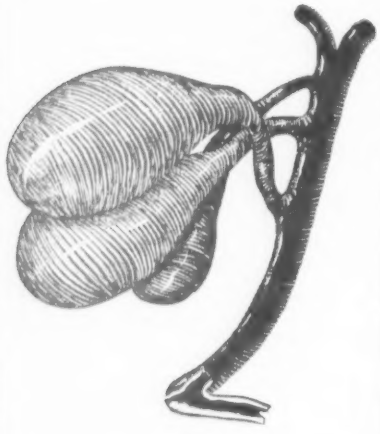

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TABLE OF CONTENTS

VOLUME 103 JANUARY 1959 NUMBER 1

EDITORIALS

PAGE

Interesting Observations of the Aging Process
George Burch, M.D., New Orleans 1

ORIGINAL ARTICLES

Serum Triglycerides in Coronary Artery Disease
Margaret J. Albrink, M.D., and Evelyn B. Man, Ph.D., New Haven, Conn. 4

Regulation of the Pulmonary Ventilation in Pulmonary Emphysema
Alvan L. Barach, M.D., New York 9

Relation of Azotemia to Blood "Ammonium" in Patients with Hepatic Cirrhosis
Leslie T. Webster Jr., M.D., and George J. Gabuzda, M.D., Cleveland 15

The Indeterminate Pulmonary Infiltration—Our Diagnostic Dilemma
James H. Sands, M.D., F.C.C.P., Covina, Calif.; Dale M. Schulz, M.D., Indianapolis, and Lieut. Col. Elmore M. Aromstam (MC), U. S. Army 23

The Post-Myocardial-Infarction Syndrome
William Dressler, M.D., New York 28

Clinical Experience with the Use of Neomycin in Hepatic Coma
William W. Faloon, M.D., and Curtis J. Fisher, M.D., Syracuse, N. Y. 43

Some Less Familiar Roentgen Manifestations of Intrathoracic Histoplasmosis
Benjamin Felson, M.D., Cincinnati 54

The Varied Clinical Manifestations of Coxsackie Virus Infections
Robert B. Gordon, M.D.; Edwin H. Lennette, M.D., Ph.D., and Rachel S. Sandrock, M.D., Berkeley, Calif. 63

Cell Counts in Urine
William T. Wright, A.B., Boston 76

The Results of Treatment for Obesity
Albert Stunkard, M.D., Philadelphia, and Mavis McLaren-Hume, M.S., New York 79

Studies of Proteolytic Enzymes in Cerebrospinal Fluid
Loring F. Chapman, Ph.D., and Harold G. Wolff, M.D., New York 86

Thymoma and Hemopoietic Insufficiency
Edwin R. Fisher, M.D., and F. D. Beyer Jr., M.D., Pittsburgh 95

Thrombotic Thrombocytopenic Purpura
Herbert A. Burke Jr., M.D., and Robert C. Hartmann, M.D., Nashville, Tenn. 105

Bronchiectatic Destroyed Lobe as a Complication of Intrathoracic Goiter
Joseph Rakower, M.D., and Pinkhas Wayl, M.D., Jerusalem 113

Lethal Midline Granuloma of the Face
Nolan Resnick, M.D., and Philip V. Skerrett, M.D., Philadelphia 116

The Marfan Syndrome
John W. Roark, M.D., Alexandria, Va. 123

Staphylococcal Bacteremia and Osteomyelitis Successfully Treated with Novobiocin
M. Clark Silverthorne, M.D., Denton, Texas 133

Repair of Ruptured Interventricular Septum Complicating Acute Myocardial Infarction
Martin D. Shickman, M.D.; Josh Fields, M.D., and Morton Lee Pearce, M.D., Los Angeles 140

EVOLUTION OF MODERN MEDICINE

Calorimetry
Russell M. Wilder, M.D., Ph.D., Rochester, Minn. 146

CONTRIBUTIONS OF BASIC SCIENCE TO MODERN MEDICINE

Current Views on the Pathogenesis and Treatment of Wilson's Disease
J. M. Walshe, M.R.C.P. (London), Cambridge, England 155

BOOKS

Reviews by Dr. William B. Bean and Others 162

A. M. A.
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VOLUME 103 JANUARY 1959 NUMBER 1

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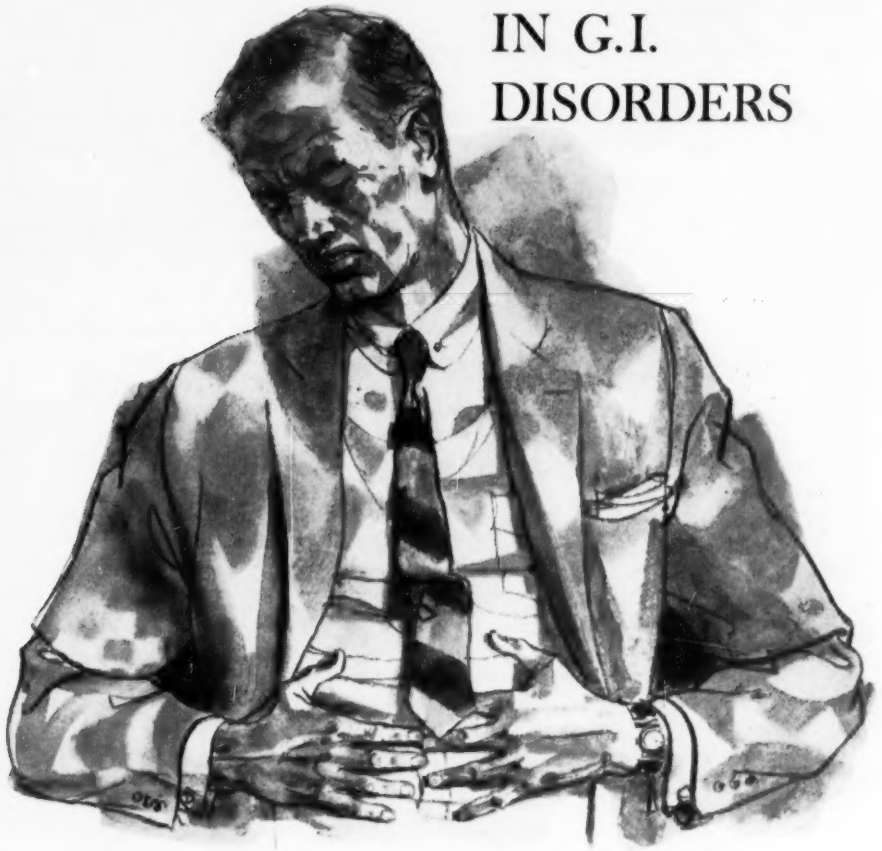

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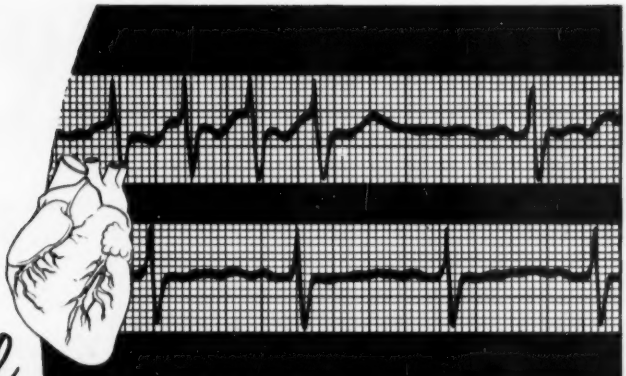

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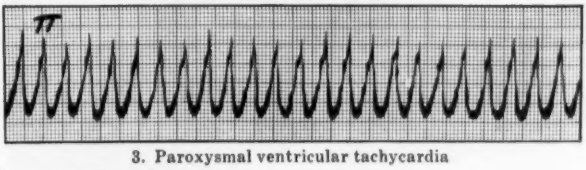

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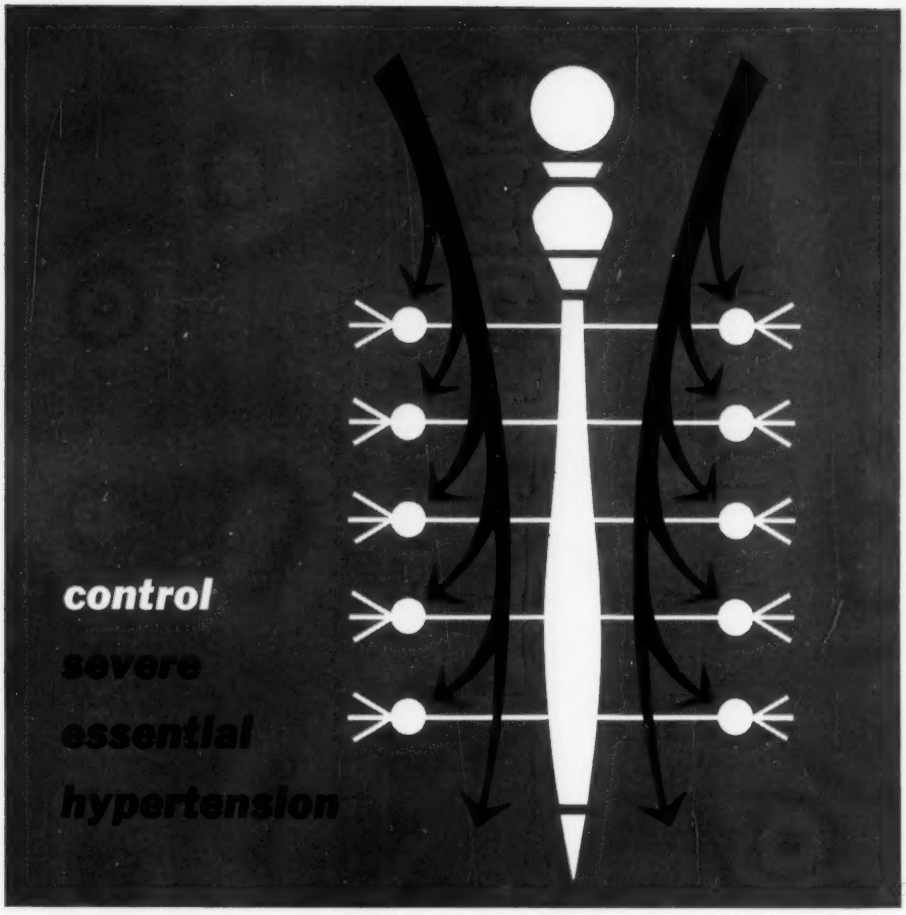

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Editorials

Interesting Observations of the Aging Process

Unfortunately, the long life span of man makes it impossible for an investigator to study him throughout his average lifetime. Only segments of man's life are available for study by any one man, and unless succeeding teams of investigators with adequate interest can be gathered to trace the longevity of a group of people, the study will be incomplete. Nevertheless, there are many interesting and important problems available for study in other living models, and so those who desire to study fundamental aspects of the aging process need not fret or be concerned with high costs of experiments. For example, various aspects of aging can be studied in lower forms of living things with short life spans. Once the living experimental model with a relatively short life has been selected, a reliable manifestation of aging offers in next difficulty. A phenomenon which definitely reflects the aging process is not easy to select and record accurately, but the simplest and apparently most reliable measure and one most likely to reflect the aging process is the duration of life itself. To illustrate such studies, it may be of interest to describe a few fundamental observations of aging of lower animals with relatively short lives in which the duration of life was used as the index of aging.

Nutrition

McCay and others [1] were interested in the influence of nutrition on longevity and the rate of aging. They showed that newborn rats and other mammals fed a well-balanced diet low in total calories developed into small animals with delay in maturation. Almost invariably the life span of these animals was increased considerably. Rats with an expectancy of two years lived one thousand days. Pigs from the same sty fed large quantities of food grew rapidly, became large and fat, and matured early. Others from the same sty fed inadequate quantities of food remained scrawny and matured late. But the skinny pigs invariably lived much longer than the fat and overfed large ones. The same was found to be true for cattle, birds, trout, plants, and even one-cell animals.

Overfeeding on the one-cell animal, Tokophrya infusionum, resulted in large animals with large cytoplasmic mass, a macronucleus with honeycombing, accumulation of a large quantity of waste products in the cytoplasm, and early death, with reproductive decline and eventual extinction of the colony.[2] On the other hand, a separate underfed colony resulted in relatively small but vigorous highly fertile animals with relatively small cytoplasmic mass and long survival time, greatly exceeding that of the overnourished group. The higher the ratio of nuclear

Submitted for publication Aug. 6, 1958.

mass to cytoplasmic mass, the greater the longevity of the animal. As stated by McCay,[1] "The thin rat goes to the funeral of the fat rat."

Interestingly enough, in all of these studies, the quantity of feeding, whether restricted or excessive, did not change the survival time once maturation had been reached. Underfed animals that were late in reaching maturation lived a longer than average life span even if overfed after attaining maturation. Whether or not such findings apply to man is not known; however, if they do not apply to man he will be the only exception among a large variety of living things studied thus far. These studies should interest not only pediatricians and nutritionists but all doctors and biologists. What makes overfeeding prior to maturation so lethal is not known.

The paradoxical cruelties of nature are revealed in these aforementioned phenomena. For example, nature demands that birds that hatch and develop in the arctic regions of the earth must eat abundantly, grow rapidly, and mature early enough to become sufficiently strong to get on the flyways southward before they freeze and thus escape almost immediate and certain death. But at the same time, heavy eating prior to maturation results in early maturation and a definitely shorter life span, or a relatively early death. Such is the paradox of the laws of nature. The same is true for the wild animals of the jungle, who must grow big and strong quickly and mature early in order to protect themselves from predators, even though this rapid early growth shortens their lives. Fortunately, man, with laws to protect the weak and unfit as well as the strong, can afford to grow slowly.

Reproduction

A fresh-water flatworm, Stenostomum incaudatum, reproduces by dividing into two parts, either into an anterior third and posterior two-thirds or into a posterior third and anterior two-thirds. The respective parts then grow into adult worms. Sonneborn [3] showed that the adult worms that develop from the anterior third live about thirty-five days, while those that develop from the posterior third live about sixty-five days. The reason for the greater longevity of adult worms derived from the posterior third is not known, but it must be an interesting and fundamental biologic phenomenon. Why do two different parts of the body of the worm confer such extreme differences in life span? This important problem is awaiting study. The mechanism must be concerned with important phases of the aging process.

Bethell [4] made an important observation in a study of a species of rotifer with a life span of about fifteen days. This animal is parthenogenic, and so one egg transmits pure genetic characteristics to all offspring. A selected egg was allowed to hatch, and the eggs of the resultant adult were separated into two groups, those laid during the first two to five days of the mother's reproductive life and those laid during the tenth to twelfth days of the mother's reproductive life. As these eggs hatched, the eggs from each succeeding orthoclones were separated in the same way. All animals were watched and the duration of their lives recorded. By selection of eggs from young mothers of successive generations, offspring that lived as long as one hundred five days instead of fifteen days, a sevenfold increase in longevity over that of the original animal, were finally developed. On the other hand, the orthoclones developed from the eggs of the old mothers gradually diminished in life span with succeeding generations until the race became extinct. Interestingly, when the earliest eggs were selected from the orthoclones of old mothers of a line about to become extinct, longevity was not only restored, but, with continuation of such selection in succeeding generations, animals were finally

developed that would live over one hundred days. The duration of life span could be worked back and forth as desired.

What is it, then, that the young mothers provided in their gametes which transmitted vigor and longevity to the offspring and that the old mothers lacked in sufficient quantity to even maintain the species? This unknown mechanism must be an important phenomenon of nature related to aging. It is yet to be determined whether or not men of young mothers live longer than men of old mothers, a problem awaiting study. The answer may be of considerable importance to mankind.

Endocrinology

Wigglesworth, of Cambridge, England, cited by Bethell,[4] noted that removal of the heads of the larvae of a blood-sucking insect, Rhodnius, caused immediate molting of the larvae to the pupal stage and rapid passage to the adult moth, resulting in a shorter life span of the animal. He reasoned and later showed that the head contained a source of hormone which held the larvae and pupa in their respective stages until growth was completed before metamorphosis to the next stage of development occurred. Two small pedunculated bodies, corpora allata, located on the dorsum of the brain were shown to be the source of this hormone. This hormone was found to be present in many insects. Implantation of the corpora allata beneath the exoskeletion of larvae or pupae delayed or interrupted metamorphosis to the next stage, produced large animals, and prolonged the life span of the animal.

Carol Williams of Harvard showed that grafting a decapitated adult silkworm moth, Bombyx mori, with a life span of ten days, to the pupa of another animal inhibited metamorphosis of the pupa and resulted in survival of the adult moth for ten or more months. He then found the abdomen of the adult moth to have a depot of large quantities of the hormone from which hormone was circulated into the pupa, with resultant symbiotic coexistence and "perpetual" life of the adult and pupa. Crude extracts of golden yellow oily hormone have been isolated and shown to be extremely potent upon injection into other insects. Recently this hormone has been found to exist in many animals, including mammals. The hormone must be of considerable importance in the animal kingdom and may be concerned with the aging process.

These selected fundamental discoveries are presented to reveal some of the problems of the aging process, to indicate interesting avenues of study, to point out the value of lower animals as a tool for the study of aging and other fundamental biologic phenomena, and to call attention to the wonders of living processes. Studies of this nature should interest medical investigators, both young and old, including aging investigators entering retirement with limited laboratory facilities.

GEORGE BURCH, M.D.

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Serum Triglycerides in Coronary Artery Disease

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The identification of cholesterol as a constituent of atheromatous plaques has aroused recurrent waves of suspicion that lipid metabolism is in some way responsible for the development of atherosclerosis and coronary artery disease. Lipids are transported in serum as constituents of three major classes of compounds: cholesterol and its esters, phospholipids, and triglycerides or neutral fat. Most investigations in recent years have centered about the notion that serum cholesterol plays a causative role in the development of coronary artery disease in spite of numerous studies focusing attention on triglycerides. Included in these studies are reports of increased turbidity, increased and prolonged chylomicronemia, and increased ratio of β- to α-lipoproteins. Although triglycerides rather than cholesterol are chiefly responsible for turbidity of serum and constitute an important fraction of β-lipoproteins, the quantitative estimation of triglycerides has been largely neglected in studies of serum lipids in coronary artery disease.

The present research was undertaken to observe the interrelations of the three major serum lipid fractions [1-4]; their interrelations had been studied in certain metabolic disorders in 1943.[5,6] The neglected fraction, triglycerides, appeared to be most frequently elevated in coronary artery disease.[7]

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From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service, the Grace-New Haven Community Hospital.

This investigation was supported (in part) by research Grant H-3498 from the National Heart Institute and research Grant A-392 from the Institute of Arthritis and Metabolic Diseases, Public Health Service.

Materials and Methods

The subjects were 100 patients with a history of a documented myocardial infarction 1 day to 12 years previously, confirmed by electrocardiographic studies and laboratory and clinical findings. The patients were obtained during the past five years from the clinics and inpatient services of the Grace-New Haven Hospital, and we include all patients meeting the above requirements whose physicians requested lipid determinations. The 100 patients, 82 men and 18 women, ranged from 21 to 78 years of age, the greatest number being in the 50's. Eleven were diabetics.

Control subjects consisted of a heterogeneous group of healthy medical school students and personnel, healthy industrial workers, and hospital patients without evidence of focal vascular disease and without known metabolic disorders. Ages ranged from 20 to 78.

Blood was drawn before breakfast, and the serum was analyzed for total fatty acids after hydrolysis, for total cholesterol, and for lipid phosphorus.[8] Triglyceride fatty acids were estimated by subtracting the fatty acids attributed to cholesterol esters and phospholipids from the total fatty acids. Cholesterol-phospholipid ratios were not remarkable.

Normal ranges for cholesterol and triglycerides were established as two standard deviations above

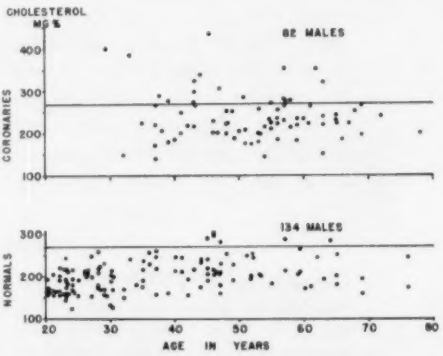

Fig. 1.—Concentration of cholesterol by age in the sera of 82 men, including 9 diabetics, with a history of myocardial infarction (upper graph) and of 134 normal men (lower graph). In each a horizontal line indicates the upper limit of normal, 269 mg. %.

and below their mean concentrations in the sera of 92 healthy men and women between the ages of 20 and 29. The effects of both age and disease are assessed against this group of young adults.

Results

Figure 1 shows the concentration of cholesterol by age in the sera of 82 male patients and of 134 normal men. A horizontal line is drawn at the upper limit of normal, 269 mg. %. Only 18% of the coronary patients had cholesterol concentrations exceeding this figure. With age, cholesterol increased slightly in the normal population. Previous studies have shown this rise to be characteristic of only a portion of the population rather than an inevitable attribute of aging.[8-10] Decade by decade, the difference between the coronary and normal groups was not significant except in the fourth decade.

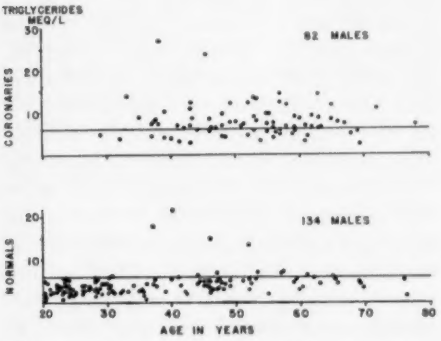

Fig. 2.—Concentration of triglyceride fatty acids by age in the sera of the same persons depicted in Figure 1. Horizontal lines indicate the upper limit of normal, 5.9 mEq. per liter.

Figure 2 shows the concentration of triglyceride fatty acids in the sera of 82 male coronary patients and in 134 control male subjects. A horizontal line is drawn at 5.9 mEq. per liter (about 175 mg. %), representing the upper limit of normal. In spite of sporadic high values and a gradual increase in triglyceride concentration with age, most of the normal values fall below this line. In contrast, 70% of the male coronary patients had triglyceride concentrations above 5.9 mEq. per liter. Despite the small numbers in each decade, the differences between the means of the normal and the coronary patients were significant at the 1% level in the 30's, and at the 5% level in each decade from 40 to 70. The mean increase in triglycerides was about 4 mEq. above the normal mean, and only two of the elevated triglycerides exceeded 20 mEq. per liter, the concentration necessary for visible gross lactescence in postabsorptive serum.[11] Most of these sera, therefore, were clear or only slightly opalescent.

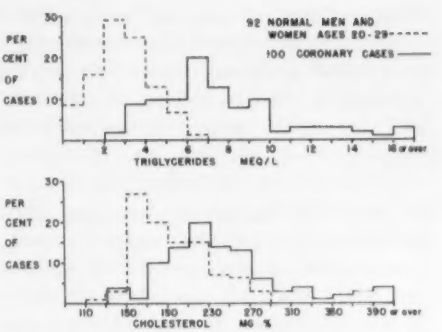

Fig. 3.—Frequency distribution of concentrations of triglyceride (upper graph) and cholesterol (lower graph) in the sera of healthy young adults and of 100 coronary patients, including 18 women and 11 diabetics.

Figure 3 compares the frequency distribution of cholesterol and triglycerides in normal and coronary populations. Triglyceride concentrations for the normal population lie almost entirely below the upper limit of normal of 5.9 mEq. per liter. Although

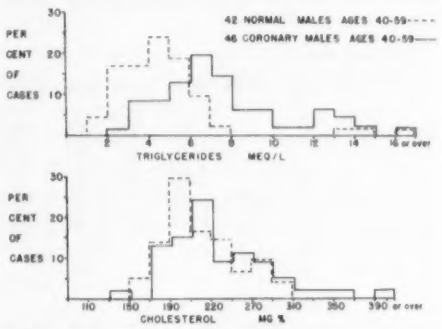

Fig. 4.—Frequency distribution of concentration of triglyceride (upper graph) and cholesterol (lower graph) in the sera of normal male subjects aged 40-59 and of male nondiabetic coronary patients aged 40-59.

values for some coronary patients are found within the upper part of the normal range, the greatest frequency occurs above this concentration. Serum cholesterol concentrations are clearly greater in the coronary group, but there is a large area of overlap.

In Figure 4 a similar comparison is made, this time achieving greater homogeneity of both the normal and the coronary populations by selecting only normal male subjects aged 40-59 and male nondiabetic coronary patients in the same age range. There is still a clear difference between the normal and coronary groups with respect to triglycerides, but separation is less complete than in Figure 3 because of the higher triglyceride values of the normal population in this age group. The lower part of the figure shows that any segregating power of cholesterol present in the younger age group appears to be lost here, with almost complete overlapping of the upper limits of the two distribution curves. While the coronary group has a higher mean cholesterol than the normal group of the same age, the individual observations are usually well within the range of normal. This is in accord with the experience of other investigators.

Analysis of the data from the entire male coronary and normal populations except the diabetics for a discriminate function of triglycerides revealed that the triglyceride concentration best separating the coronary from the normal male population was 5.5 mEq. per liter, a figure only slightly below

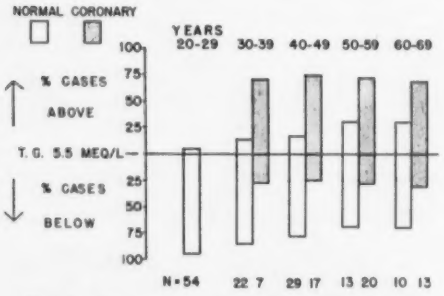

Fig. 5.—Per cent of normal and coronary nondiabetic men in each decade having concentrations of serum triglycerides above and below 5.5 mEq. per liter.

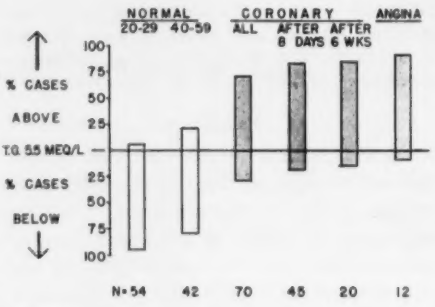

Fig. 6.—Per cent of persons having concentrations of serum triglycerides above and below 5.5 mEq. per liter. Shading indicates coronary artery disease. The last bar represents 12 patients with angina pectoris who had not had a myocardial infarction.

the upper limit of normal, 5.9. Figure 5 shows decade by decade the per cent of normal men and coronary men having triglyceride concentrations above 5.5 mEq. per liter, shown above the horizontal line, and the per cent having triglyceride concentrations below 5.5, shown below the horizontal line. Normal men fell almost entirely below this line in the 20's. With increasing age there was a gradual increase in triglycerides until in the 50's and 60's 30% of the normal male population had serum triglycerides exceeding 5.5 mEq. per liter. In contrast, 70% or more of the coronary population had serum triglyceride concentrations greater than 5.5 mEq. per liter, and this was constant at all ages examined.

Whether a more careful screening of the normal population would reduce the false positives or whether high triglycerides in this group are predictive of future vascular disease is not known. It was possible to reduce the number of coronary patients falling in the normal range by excluding those determinations made during the acute phase of illness following the infarction and diminishing therefore the possible influence on triglycerides of acute illness, inadequate caloric and protein intake,[12-14] anticoagulants, and other drugs. Figure 6 summarizes the previous slide in the first three bars, regarding normal young adults, normal men 40 to 59 (the age range of greatest suscepti-

bility to myocardial infarction), and all coronary cases. The fourth and fifth bars show that if determinations during either the first eight days or the first six weeks after an infarction were excluded, 84% of the patients had triglycerides above 5.5 mEq. per liter. The last bar demonstrates that this concentration was exceeded by 11 of 12 patients with angina pectoris who had not had a coronary and were therefore not included in the present study.

High triglycerides could not be attributed to dietary fat or excess calories. Excluding patients studied during the first eight days, total calories were limited and fat restricted to 60 gm. a day or less in 24 of 45 male nondiabetic patients. Triglycerides were elevated in 19 of the 24; cholesterol, in 8. Indeed in certain persons an inverse relationship between cholesterol and triglycerides was apparent after a low-fat diet. Such a patient, as an example of others, is demonstrated in Figure 7. The first determination was made six months after an acute myocardial infarction. Following initiation of a diet very low in fat but adequate in protein, cholesterol declined somewhat, but a year later his triglycerides had risen markedly. Others have reported similar increases in triglycerides in response to low-fat high-carbohydrate diets.[15,16] The treatment of coronary artery disease with low-fat diets, currently in common practice, might therefore in some instances raise the serum triglycerides, an effect which might be undesirable if triglycerides have the significance suggested by the present study.

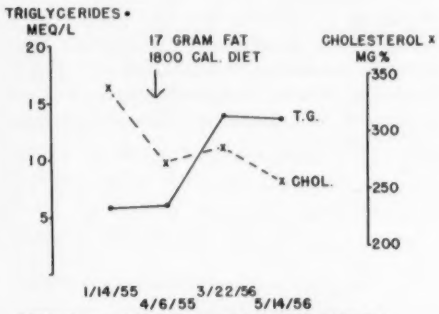

Fig. 7.—Concentration of triglycerides and cholesterol in the serum of one patient before and after institution of an 1,800 Cal. diet containing 17 gm. of fat and 80 gm. of protein. The patient had had a myocardial infarction six months before the first determination.

Summary

In summary, elevations of serum triglycerides above 5.5 mEq. per liter (about 160 mg. %) occurred in only 5% of normal young adults, in at most 30% of normal men over 50, and, if the effects of acute illness were excluded, in 85% to 90% of patients with coronary artery disease. Few, if any, other lipid measurements which have been reported effect such a clear-cut separation between the normal and coronary subjects.

The present report suggests that an error in the metabolism of triglycerides is the lipid abnormality operative in coronary artery disease. It may be that other findings commonly reported in this disease, such as increased cholesterol, increased low-density lipoproteins rich in triglycerides, and prolonged and intensified alimentary lipemia,[17,18] are secondary to decreased efficiency of triglyceride utilization with resulting accumulation of triglycerides in plasma. It is tempting to speculate on the significance of these findings in relation to the energy metabolism of the heart, particularly in the light of recent evidence that fat is an important source of fuel for the normal myocardium, that triglycerides are turned over with great rapidity by heart tissue, and that lipoprotein lipase occurs in high concentration in myocardial tissue.[1,3,4,7,19-23] Future work may orient the findings reported here within the framework of triglyceride metabolism as it fluctuates with changing demands of the total body economy from moment to moment and over the years.

Dr. Colin White, of the Department of Public Health, Yale University, performed the statistical analyses.

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Regulation of the Pulmonary Ventilation in Pulmonary Emphysema

Priority of Respiratory Effort Over the Respiratory Center

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Although the respiratory center of normal persons responds to carbon dioxide with a predictable increase in minute volume of ventilation, the patient with pulmonary emphysema manifests a relatively lower increment of ventilation to inhalation of a given carbon dioxide percentage (Scott [1]). This difference in response has been commonly explained on the basis of impairment of the sensitivity of the respiratory center, due to the presence of hypercapnia in this entity.[2-5] However, other investigators have recently presented sound physiologic evidence which suggests that the lowered ventilatory response to carbon dioxide is caused by limitation in the maximal breathing capacity and that there is no demonstrable impairment of the respiratory center itself.[6-8] As a result of analyzing previous data from our clinic as well as findings of more recent investigations,[9,10] I propose the concept that the work of breathing, including the factor responsible for respiratory effort, frequently takes precedence over the activity of the respiratory center and, at times, the carotid sinus; therefore, inhalation of increased percentages of carbon dioxide in the atmosphere does not reveal insensitivity of the respiratory center, nor is the ventilatory response correctly explained as the consequence of hypercapnia.

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From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital.

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Elevated Carbon Dioxide Content of Arterial Blood in Pulmonary Emphysema

The content of carbon dioxide in the arterial blood is frequently elevated in patients with diffuse obstructive pulmonary emphysema. When oxygen is administered to these patients in a program of gradually increasing oxygen concentrations in the atmosphere breathed, the carbon dioxide tension in the blood is progressively elevated; the patient, under this carefully regulated oxygen-therapy regimen, does not become irrational, owing to the fact, in my opinion, that the pH of the arterial blood remains relatively constant.[9-11] This characteristic response of patients with cardiac insufficiency, as well as pulmonary emphysema, is due to a decrease in pulmonary ventilation, the manifest cause of carbon dioxide retention in the blood.[12-15]

Increasing the arterial pO_2, mediated through its effect on the carotid sinus, decreases the minute volume of breathing in these cases. The lowered ventilatory volume and the associated carotid sinus stimulation appear to have a clear priority over the activity of the respiratory center in respect to its response to accumulation of blood carbon dioxide. However, this reaction cannot be accepted as evidence that the respiratory center is insensitive to increased carbon dioxide tension in the blood. A high partial pressure of carbon dioxide in the alveolar air is made use of in an adaptive mechanism that permits a lowering of the work of breathing. Furthermore, the respiratory center responds to inhalation of carbon dioxide in a manner similar to that of the normal person subjected to the same

degree of restriction in maximal minute ventilation.[8]

The compensatory adjustment to oxygen inhalation was previously described[15] as follows:

> When the anoxemia is relieved, there is a constant and marked rise in the carbon dioxide concentrations of the blood with an *even greater elimination* of carbon dioxide per breath through the congested lung. Thus, in one of the cases of congestive failure, the carbon dioxide content of the arterial blood rose from 38.4 to 69.9 volumes per cent in four days. It appears, therefore, likely that the elevation in carbon dioxide level in the blood is an adaptive change which is readily accomplished if sufficient oxygen is supplied to maintain normal metabolic activity....A decrease of pulmonary ventilation follows with a lessened sense of respiratory effort and therefore relief of dyspnea....In the second patient with fibrosis of the lung and cardiac insufficiency, the carbon dioxide in the arterial blood rose from 38.4 to 69.9 after four days' oxygen treatment, and then, as the patient improved, dropped to 48.9 volumes per cent, even though he was still breathing an oxygen-enriched atmosphere. Thus, when the function of the lung, if severely impaired, was relieved by the inhalation of oxygen, the carbon dioxide concentration in the blood and in the alveolar air became elevated, as an adaptive reaction noted above. But when the pulmonary function improved in respect to the absorption of oxygen, the carbon dioxide concentration in the blood and alveolar air diminished.

The homeostatic principle described above (1931) is still considered valid; the increased carbon dioxide in the alveolar air permitted the patient to decrease respiratory effort and, in that way, take advantage of oxygen therapy when properly administered. Richards and I[12,13] described the elimination of chlorides and the rise in base bicarbonate as a compensatory response to the retention of carbon dioxide. This so-called homeostasis breaks down when high concentrations of oxygen are abruptly administered to patients with bullous emphysema; an acidotic shift in pH, with an accompanying irrationality and a comatose state, is the result of a precipitous lowering of the pulmonary ventilation before the patient has had the opportunity to develop the compensatory measures which protect against uncompensated acidosis.[11]

The technique of giving gradually increasing oxygen concentrations, outlined in 1938,[14] has been found generally successful in the prevention of both irrationality and coma, not only in our clinic but more recently by Simpson in England[16] and by Segal et al.,[17] Bickerman and Beck,[18] and Miller, Fowler, and Helmholz in this country.[19] The fact that an acid pH, due to abrupt rise in carbon dioxide and not carbon dioxide retention itself, is the cause of adverse mental changes has been recently confirmed by Motley.[20] In the patient who has already developed severe respiratory acidosis, hypoxia and fatigue of the respiratory musculature contribute to a near-shock state in which the patient is manifestly seriously ill. Hypoventilation must of course be corrected. However, in most patients with carbon dioxide elevation in the arterial blood (without acidosis), the decreased work of breathing, and the associated lowered minute volume of breathing engineered by oxygen inhalation, not only has a priority over the respiratory center's response to carbon dioxide but is itself beneficial. In Cherniak and Snidal's studies[8] normal subjects were found to respond to carbon dioxide inhalation with a ventilatory response similar to that of the emphysematous patient when restriction in their maximal breathing capacity (M. B. C.) was artificially produced. In each instance, increase in M. B. C. was followed by increase in ventilatory volume when a comparable percentage of carbon dioxide was inhaled. The so-called insensitivity of the respiratory center to carbon dioxide, as well as apparent causally related hypercapnia, appears to be a coincidence related to impairment in mechanical ventilatory capacity.

It seems to me that a more tenable explanation of the maintenance of high arterial and alveolar carbon dioxide is related to the concessive character of the respiratory center in respect to the factors which lower the total work of breathing and diminish the energy expended in ventilating the lungs. A lowered oxygen consumption results in the beneficent consequence of reduced min-

ute volume of breathing, and diminished carbon dioxide production as well. In compensated cases of carbon dioxide retention, the superior sensitivity of the carotid sinus and the aortic bodies to oxygen takes precedence over the response of the respiratory center to increasing carbon dioxide tensions.

Physical Methods of Enhancing Efficiency of Pulmonary Ventilation

The substitution of diaphragmatic breathing for upper thoracic respiration has been promoted by such procedures as pneumoperitoneum, emphysema belt, abdominal sand bag, and breathing exercises. The studies of various investigators who have described the value of the increased movement of the diaphragm provided by these methods have been recently reviewed.[9] Of special pertinence to our thesis is the finding that a marked lowering of the minute volume of breathing was produced in a large group of patients when excursion of the diaphragm was increased 3.0 cm. by placing them in the head-down position; in short experiments, hypoxia as well as hypercapnia was unchanged.[21] This response thus constituted plain evidence of the priority of relief of respiratory effort over the activity of both the respiratory center and the carotid sinus. The relief of dyspnea and diminished oxygen consumption constituted evidence of diminished work of breathing. In some cases, the oxygen removal rate per liter of ventilation was increased. However, when the oxygen consumption was markedly lowered the so-called ventilatory equivalent was little altered or even diminished. An example of the most radical changes in pulmonary function produced by a change from the sitting-erect to the head-down position, thorax tilted 18 degrees, is seen in Table 1. It will be seen that the minute volume of ventilation decreased to a greater extent in the head-down position (from 12.3 to 7.4 liters per minute) than when 100% oxygen was inhaled (10.3 liters). However, when the effect of breathing oxygen was added to that of diaphragmatic breathing, the ventilation decreased to 6.1 liters per minute.

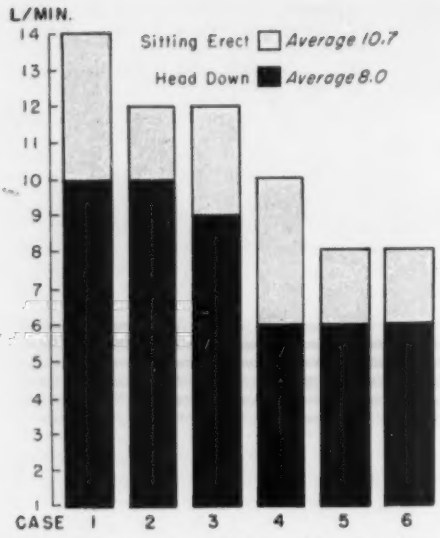
TABLE 1.—*Changes in Pulmonary Ventilation and Oxygen Consumption Induced by Head-Down Position and Breathing One-Hundred Percent Oxygen* *

	Air, Min. Vol.		Oxygen, Min. Vol.	
	Sitting	Head-Down	Sitting	Head-Down
P. V., L.	12.3	7.4	10.3	6.1
O_2 consumption, cc.	460	330	410	280
O_2 per liter ventilation, cc.	33	27	40	22

* The energy expended in the work of breathing was lowered 30% by the substitution of diaphragmatic breathing for upper thoracic respiration. The oxygen consumption and the oxygen removed per liter of ventilation during the inhalation of 100% oxygen cannot be considered accurate because of the absorption of oxygen by the blood and tissues in short-term experiments.

When this patient was sitting erect and using the upper costal and accessory neck and shoulder girdle muscles for breathing the oxygen consumption was 460 cc. per minute. With diaphragmatic breathing in the head-down position the figure dropped to 330 cc. per minute. This response gives evidence of aeration of better-perfused lung near the hilum, with diminished ventilation of bullous peripheral segments of the lung. Favorable effects of diaphragmatic breathing on respiratory function were also reported by Miller.[22] In patients with obstructive pulmonary emphysema who do not respond to the head-down position with a lowering of the ventilation, the disease may be more diffuse and extensive or cardiac failure may be present.

In any event, a fall of 20% to 30% in oxygen consumption and pulmonary ventilation is evidence of a marked diminution of the work of breathing. In a group of similarly studied patients the arterial pO_2, pCO_2, and pH were not changed during short-term studies; the response in six patients who manifested an average decrease in pulmonary ventilation, from 10.7 to 8.0 in one minute is shown in the Figure.[21] The thorax was tilted 18 degrees.



The pulmonary ventilation with the thorax tilted head down and breathing air decreased from an average of 10.7 to 8.0 liters per minute in six patients with pulmonary emphysema. Data from Barach and Beck.[21]

Mechanically Induced Increase in Reserve-Volume Respiration

In studies of Barach and Beck [10,21] on the effects of mechanical increase of reserve-volume respiration additional evidence of the priority of a lowered ventilatory response has been found. Compression of the lower thorax and upper abdomen was accomplished by means of a pneumatic jacket; the patient's exhaled air was transmitted to a sensing device which activated a motor-blower unit. The air pressure applied during the expiratory cycle produced an increased tidal air, lung volume being decreased at the end of expiration. The patient's cycling rate was determined by his over-all response to chemical factors and proprioceptive reflexes from the lungs and moving framework of the chest wall.

The response of a group of these patients was a lowering in the rate of breathing and in the total ventilation. It has been well established that slowing of the respiratory rate results in a considerable reduction of viscous resistance and of the work of breathing.[9] The blood pO_2, pCO_2, and pH

TABLE 2.—*Arterial Blood Gases and pH During Patient-Cycled Pneumatic Breathing Air* *

	Arterial Blood		
	pH	pCO_2	O_2 Saturation
Before P. B. A.	7.45	52	85
After 25 min. P. B. A.	7.46	49	85
After 55 min. P. B. A.	7.43	52	84

* Arterial blood gases and pH preserved at or near control level despite 20% decrease in pulmonary ventilation.

in one of these cases, studied before and at varying intervals during reserve-volume breathing, revealed that arterial hypoxia (85% oxygen) was maintained at or near the control level, as were the pCO_2 (52 to 49 mm. Hg) and the pH (7.45 to 7.46) (Table 2).*

In some, although not in all of these patients with emphysema, the increased efficiency provided by lessened dead-space ventilation, i. e., increased reserve tidal air, resulted in marked relief of a previously heightened and burdensome ventilation. A priority over both the hypoxic stimulus to the carotid sinus and the carbon dioxide stimulus to the respiratory center was again plainly revealed, as it was in the behavior of patients whose thorax was tilted head down. When institution of diaphragmatic breathing was accomplished by placing a 25 lb. buckshot or sandbag on the abdomen a similar decrease in minute volume of breathing was observed.

Comment

A *decreased* pulmonary ventilation has the special advantage in the emphysematous subject of markedly decreasing the amount of carbon dioxide produced. Since hyperventilation of 15 liters per minute may require the same amount of respiratory work that a normal person performs breathing at more than double that volume (McIlroy and Christie [24]), the initiation of a lower ventilation as a result of more efficient aeration of better parts of the lungs

* The blood gas measurements were provided by Dr. Alfred M. Fishman.

is followed by a beneficial cycle of lower carbon dioxide production and hence a diminished ventilatory requirement. Although the regulation of the total pulmonary ventilation is admittedly the result of a summation of many factors,[25] an evaluation of certain procedures that were of therapeutic value to the patient provided the opportunity of presenting the thesis here described.

The response of the patient with pulmonary emphysema to a *regulated* oxygen program is characterized by a decrease in the volume of breathing; the resultant increase in arterial carbon dioxide tension is not considered a manifestation of insensitivity of the respiratory center to carbon dioxide but rather an indication of a priority of the mechanism that leads to reduction in the work of breathing, and consequently, dyspnea. This mechanism includes the sensitivity of the carotid sinus to arterial hypoxia, adaptive compensatory elimination of carbon dioxide at high partial pressures in the alveolar air, and a decrease in oxygen requirement and carbon dioxide production. The previously described homeostatic nature of the response of the patient with pulmonary emphysema to oxygen inhalation has received support in a recent discussion of Riley,[26] as well as by the acclimatization studies of Riley, Otis, and Houston.[27]

The studies of Cherniack and Snidal[8] and others[6,7] indicate that these patients respond to inhalation of carbon dioxide in a manner similar to normal persons who have imposed upon them a comparable restriction in maximal breathing capacity; the concept of insensitivity of the respiratory center to carbon dioxide as a result of hypercapnia is questionable and, therefore, the therapeutic proposals to blow off carbon dioxide routinely by hyperventilation devices. The homeostatic equilibrium of these patients may indeed be altered, but the clinically well-adapted patient (i. e., without uncompensated acidosis) is not, in my opinion, benefited by artificial reduction in pCO_2 and bicarbonate.

The substitution of diaphragmatic for thoracic respiration is accompanied by a sharp reduction in ventilatory effort and in the volume of breathing, without reduction in hypercapnia or hypoxia. The priority of factors which decrease the work of breathing over chemical stimuli to the respiratory center and to the carotid sinus was also demonstrated in cases in which reserve-volume respiration was increased by a pneumatic breathing aid, the volume of breathing being regulated by the patient through employment of a sensing device. The behavior of a group of these patients also revealed the characteristic lowering in the rate and minute volume of breathing.[28]

Summary

Among the factors which regulate the pulmonary ventilation in patients with pulmonary emphysema, the degree of respiratory effort and the associated energy involved in breathing play a significant role. Procedures which enhance the efficiency of alveolar ventilation frequently result in a marked lowering of the minute volume of breathing, despite the continued presence of hypercapnea. Evidence is presented which indicates that this response is not due to insensitivity of the respiratory center but rather to a priority of the factors which diminish the heightened work of breathing and the resultant dyspnea.

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Relation of Azotemia to Blood "Ammonium" in Patients with Hepatic Cirrhosis

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Oliguria and azotemia may accompany the development of hepatic coma in patients with severe liver disease, and they are frequently ominous prognostic signs. Since urea from the circulating blood enters the gastrointestinal tract where it can be degraded to ammonium by the action of bacterial urease,[1] urea may be capable of contributing indirectly to the increased concentration of ammonium found in the blood of some patients with liver disease. Increased circulating urea might then be considered with other nitrogenous substances capable of inducing impending hepatic coma in patients with severe hepatic disease.[2-7] This investigation was done to determine the influence of azotemia upon the blood ammonium levels in patients with hepatic disease and to evaluate the relation of azotemia to hepatic coma.

Materials and Methods

Four groups of patients were studied. One group consisted of six patients with azotemia but without liver disease (Table 1). A second group consisted of four patients with azotemia and chronic hepatic disease (Table 2). These four patients were mentally alert and displayed none of the neurological signs of impending hepatic coma when the studies were initiated. The two additional groups consisted of 24 hospitalized patients without evidence of hepatic disease or azotemia (urea nitrogen concentrations below 25 mg. per 100 ml. of blood) and 27 patients with hepatic cirrhosis and normal blood urea nitrogen concentrations. Clinical and laboratory data pertinent to the latter two groups of patients have been published.[8]

The patients were hospitalized in the medical wards of Cuyahoga County Hospital. Their estimated daily protein intakes ranged from 0-100 gm., except for those with hepatic disease and azotemia from whom protein was withheld for at least 48 hours prior to blood sampling. Neurological evaluations were made frequently, with special regard for the presence or absence of confusion, "flapping" tremor, and coma. These findings were graded from first to fourth degree, first degree indicating a mild and fourth degree, a severe disturbance for each entity.[9]

Blood samples were obtained within five minutes of each other from an extremity vein, a brachial or carotid artery, and a superior jugular bulb. These samples were analyzed for ammonium (NH_4-N) content by a modified Conway technique.[6,10] Arteriovenous NH_4-N concentration differences were calculated for the extremities and for the brain.

Patients had not received nitrogenous foods, supplements, or medications for at least 12 hours prior to blood sampling. None had evidence of gastrointestinal bleeding, clinical shock, or blood pressure readings below 90 mm. of mercury during these studies. Antibiotics were given only as indicated.

Aspirates of mixed gastric and duodenal juices were obtained through a sterilized Levin tube inserted through the nose in a routine manner. The aspirates were analyzed for NH_4-N content by the method indicated above. The bacteriology reported may represent that of either the upper respiratory or the gastrointestinal tracts, or both.

The method of Myers or that of Owings and Mandel was employed for the determination of blood urea nitrogen concentration. The latter technique was used to determine urea nitrogen in

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TABLE 1.—*Clinical and Laboratory Data for Six Patients with Azotemia*

Patient	Age Sex	Clinical Diagnosis	Physical Examination	Mental State	Urine	Serum SBP, % Retention	Total Bilirubin, Mg/100 Ml.	BUN, Mg/100 Ml.	Blood NH_3-N, μg/100 Ml.		
									Antecub. or Femoral Vein	Artery	Jugular Bulb
1	41 M	Arteriolar nephrosclerosis *	"Uremic" frost, generalized twitching B. P. 170/120	Stuporous	S. G. 1.010; Alb. 2+; microscopic, normal	8		265	32	72	75
2	57 M	Chronic pyelonephritis	B. P. 260/150	Normal	S. G. 1.004-1.010; Alb. 1-3+; microscopic, normal	3	0.2	93	59	55	67
3	68 M	Acute & chronic pyelonephritis	Fever, B. P. 120/80	Confused	S. G. 1.008; Alb. 2+; microscopic, many WBC & bacteria	2	0.8	54	41	58	58
4	24 F	Acute pyelonephritis, chronic renal disease	Fever, pallor, periorbital edema, B. P. 175/110	Normal	S. G. 1.008-1.010; Alb. 3+; microscopic, many WBC, bact., few RBC			177	34	23	
5	17 M	Chronic renal disease, (?) etiology	Gen. clonic convulsions, B. P. 130/80	Comatose	S. G. 1.010-1.012; Alb. 4+; microscopic, normal		0.2	53	57	58	59
6	75 M	Starvation (?) chronic renal disease	Dehydrated, B. P. 110/50	Comatose	S. G. 1.012-1.016; Alb. 2+; microscopic, normal	0	1.4	125	64	67	80

* Confirmed by autopsy.

TABLE 2.—*Clinical and Laboratory Data for Four Patients with Chronic Hepatic Disease and Azotemia*

Patient	Age Sex	Diagnosis	Biopsy or Autopsy	Physical Examination	Urine	Serum SBP, % Retention	Total Bilirubin, Mg/100 Ml.	Mental State *	"Flapping" Tremor	BUN, Mg/100 Ml.	Blood NH_3-N μg/100 Ml.		
											Antecubital or Femoral Vein	Artery	Jugular Bulb
1	64 M	Cirrhosis, hepatoma, fatty kidney	Autopsy	Icterus, angiomata, ascites, edema	S. G. 1.010-1.015; Alb. 1+; microscopic, normal		4.1	Normal	0	74	120	159	125
								2d degree I. C.	2+	70	119	211	161
2	68 M	Cirrhosis, carcinoma	Hepatic biopsy	Icterus, hepatomegaly, ascites, edema	S. G. 1.025; Alb. 2+; microcopic. many WBC & bacteria	33	10.0	Normal	0	128	107	125	101
3	55 M	Cirrhosis, renal tubular necrosis, & fibrosis	Renal biopsy	Angiomata, ascites	S. G. 1.007-1.012; Alb. 2+; microscopic, many WBC	51	1.8	Normal	0	106	100	128	94
								4th degree I. C.	0	98	145	179	144
4	55 M	Cirrhosis, carcinoma	Autopsy	Hepatomegaly, ascites, edema	S. G. 1.030; Alb. 2+; microscopic, many WBC	48	1.8	Normal	0	60	104	196	170
								3d degree C.	0	58	514	699	589

* I. C. indicates impending hepatic coma; C., hepatic coma.

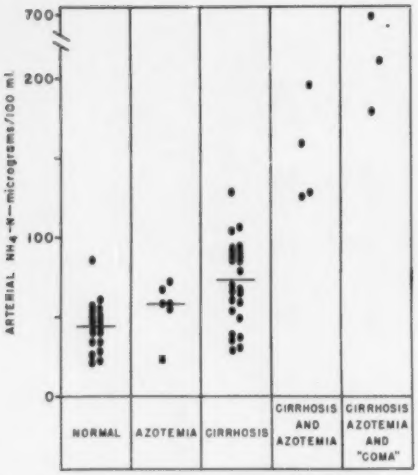

Fig. 1.—Arterial blood "ammonium" concentration.

aspirates of mixed gastric and duodenal juices.[31,32] Sulfobromophthalein (Bromsulphalein) concentration was determined in blood drawn 45 minues after the intravenous injection of 5 mg. of dye per kilogram of body weight.[33] Serum was analyzed for bilirubin by a standard technique.[34]

Results

Arterial blood NH_4-N concentrations of the six patients who had azotemia without hepatic disease were within the normal range (Fig. 1). Although the average arterial blood NH_4-N concentration was higher in patients with azotemia (55.5μg. per 100 ml.) than in the controls (43.8μg. per 100 ml.), the difference in arterial blood NH_4-N concentrations between the two groups was not statistically significant ($P=0.1$). With one exception, arteriovenous blood NH_4-N differences for the brains and extremities of the patients having azotemia without hepatic disease were within the normal range of +22μg. to −26μg. per 100 ml. (Table 1, Fig. 2).

The four alert patients with chronic hepatic disease and azotemia had an average arterial blood NH_4-N concentration which was about double the average value for the group of alert patients with cirrhosis but without azotemia (152μg. and 70μg. per 100 ml., respectively) (Fig. 1). Calculated arteriovenous differences showed an uptake of NH_4-N for the extremities, both in patients with cirrhosis and azotemia and in those with cirrhosis and normal blood urea nitrogen concentrations. The arteriovenous differences for brain were positive (an NH_4-N uptake) in the four patients with cirrhosis and azotemia (range +24 to +34, mean +29μg. per 100 ml.), whereas they varied in the control group (range −23 to +32, mean −0.3, S. D. ±2.2μg. per 100 ml.) (Fig. 2).

Ammonium nitrogen determinations were repeated in three of the four patients with chronic hepatic disease and azotemia (Table 2, Patients 1, 3, and 4) after they became confused or comatose. In each instance a higher value was found than that obtained previously (Table 2, Figs. 1 and 2). The positive arteriovenous blood NH_4-N differences for the brain and extremities increased or remained the same.

In one of the patients with azotemia and chronic hepatic disease, NH_4-N and urea nitrogen analyses were performed on samples of blood and of mixed gastric and

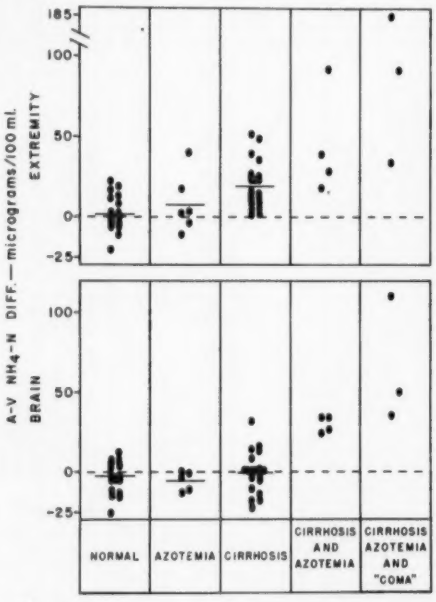

Fig. 2.—Arteriovenous blood "ammonium" concentration differences.

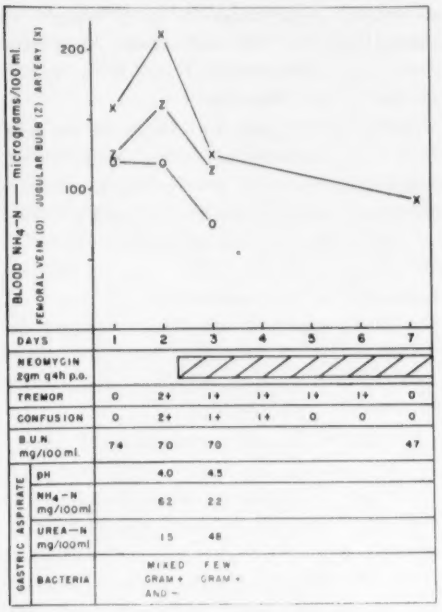
BLOOD NH_4-N — micrograms/100 ml.
FEMORAL VEIN (0) JUGULAR BULB (Z) ARTERY (X)
200
100
DAYS 1 2 3 4 5 6 7
NEOMYCIN 2gm q4h p.o.
TREMOR 0 2+ 1+ 1+ 1+ 1+ 0
CONFUSION 0 2+ 1+ 1+ 0 0 0
B.U.N. mg/100 ml. 74 70 70 47
GASTRIC ASPIRATE
pH 4.0 4.5
NH_4-N mg/100ml 62 22
UREA-N mg/100ml 15 48
BACTERIA MIXED GRAM + AND - FEW GRAM +

Fig. 3.—Data on Patient 1.

duodenal aspirates both before and after the administration of neomycin sulfate orally (Patient 1, Table 2 and Fig. 3). Before neomycin was given, NH_4-N concentrations were elevated in blood samples obtained from an artery, an extremity vein, and a superior jugular bulb. The concentration of urea nitrogen was also elevated in the arterial blood. The NH_4-N concentration in an aspirate of mixed gastric and duodenal juices was about threefold greater (62 mg. per 100 ml.) than the highest concentration obtained in six nonazotemic patients with cirrhosis (18 mg. per 100 ml.). The urea nitrogen concentration in the same sample was low, considering the elevated blood urea nitrogen concentration. Twenty hours after neomycin treatment was initiated the analyses were repeated. These revealed decreases in the NH_4-N concentrations of the blood and gastric aspirate and a rise in the urea nitrogen concentration of the aspirate, although the blood urea nitrogen concentration remained unaltered. The patient's confused mental state and flapping tremor improved after neomycin treatment, but ultimately he became confused and died.

Comment

Normal venous blood NH_4-N concentrations have been found in patients without hepatic disease in whom the blood urea nitrogen concentrations were elevated.[5] Comparable results are described here for a small group of similar patients whose arterial, superior jugular bulb, and extremity venous blood was analyzed. However, in four *alert* patients with cirrhosis of the liver and azotemia, arterial blood ammonium concentrations were increased as compared to patients in whom chronic liver disease was not associated with elevated blood urea nitrogen concentrations. These findings support the concept that increased concentrations of urea in the blood may lead to increased arterial blood NH_4-N concentrations in the presence of chronic hepatic disease.

Previous investigations provide data that allow for a possible explanation for the increased arterial blood NH_4-N concentrations associated with azotemia in patients with chronic hepatic disease. Urea in the circulating blood may enter the gastrointestinal tract and be broken down by bacterial urease into carbon dioxide and ammonium.[1,15] If the blood urea nitrogen concentration becomes elevated (e. g., in uremia), increased NH_4-N concentrations in gastrointestinal secretions may result,[1] as in the case of the patient whose data are shown in Figure 3. Some of this extra ammonium in the gastrointestinal tract may be absorbed into the portal blood and cause the portal blood NH_4-N concentration to increase.[16] Then, if the function of liver or its circulation is sufficiently impaired, decreased hepatic metabolism of portal blood NH_4-N results and the arterial blood NH_4-N concentration increases. If the formation of NH_4-N from circulating blood urea were primarily dependent upon the action of gastrointestinal bacteria, one might expect the process to be interrupted

by the administration of oral antibiotics. This is the case,[16] and in the confused patient with hepatic disease (Fig. 3) the decrease in NH_4-N and increase in urea nitrogen concentrations of the gastrointestinal secretions after he was treated with oral neomycin are consistent with such an explanation.

According to the above explanation, the increased arterial blood NH_4-N concentrations in patients with hepatic cirrhosis and azotemia result primarily from deficient hepatic conversion of an increased portal ammonium load, resulting in turn from the degradation of urea in the gastrointestinal tract. The quantity of ammonium made available by this mechanism could be considerable, since it is estimated that in normal subjects 2 gm. of ammonia per day is released into the portal circulation as a result of urea breakdown by gastrointestinal bacteria.[17] The fasting patient with chronic liver disease and azotemia would thus be physiologically similar to the patient with cirrhosis of the liver who is fed urea.[3] Because oral administration of various nitrogenous substances including urea may induce impending hepatic coma in patients with severe hepatic disease, azotemia might also be incriminated as an additional factor capable of precipitating or aggravating this syndrome in susceptible patients with hepatic disease.

It may be for the reasons stated that persistent oliguria with subsequent azotemia frequently heralds a deterioration in the patient's status and a grave prognosis. Sometimes relatively rapid increases in blood NH_4-N concentration occur in patients lapsing into hepatic coma. It seems unlikely that these increases always reflect a further decrease in hepatic function alone, because they may occur within a matter of a few hours, even in chronic hepatic disease, and are usually unaccompanied by a worsening of other tests of hepatic function. However, the combination of both decreased urea elimination by the kidneys and hepatic disease might account for these relatively sudden elevations in some cases. However, information about changes in renal function with the advent of hepatic coma and of increased blood NH_4-N concentrations is unavailable.

Although oliguria and azotemia are usually late accompaniments of hepatic coma, some patients with severe hepatic disease may have renal complications before mental or neurological symptoms appear. Three of the patients in the latter category became confused or comatose within 72 hours of the initial observations. Such a rapid development of a comatose state in patients with liver disease is not, however, limited to patients with azotemia.

Decreased hepatic metabolism of an increased portal ammonium load which is secondary to increasing blood urea nitrogen concentrations may explain, in part at least, the elevated blood NH_4-N concentrations found in patients suffering from either congestive heart failure[18] or shock.[19] In both these circumstances, hepatic and renal function are compromised. This factor must also be considered in studies designed to evaluate the efficacy of the artificial kidney for treatment of patients with hepatic coma.

The patients with cirrhosis of the liver and azotemia demonstrated positive arteriovenous NH_4-N differences for their extremities and for their brains. The findings for the extremities of three of the four patients with liver disease and azotemia were comparable to those of the patients without azotemia; the fourth patient displayed an increased ammonium uptake for the extremities. The four patients with hepatic cirrhosis and azotemia averaged significant NH_4-N uptakes for the brain, as compared to the patients with cirrhosis uncomplicated by azotemia. Arteriovenous NH_4-N differences for the brain in patients with cirrhosis and azotemia were similar to those in another group of patients previously reported, in whom an increased portal ammonium load (gastrointestinal bleeding) was associated with hepatic coma.[8]

The results of the present study provide additional rationale for the use of neomycin in the management of patients with hepatic coma,[20] since this antibiotic, by decreasing ammonium production from urea in the gastrointestinal tract, may temporarily at least effect a significant decrease in the portal ammonium load in patients with hepatic coma complicated by azotemia.

Summary

Four alert patients with chronic hepatic disease and azotemia had arterial blood NH_4-N concentrations which were significantly higher than those of a group of patients with hepatic cirrhosis and normal blood urea nitrogen concentrations. Within 72 hours each of these patients developed symptoms indistinguishable from impending hepatic coma or hepatic coma, and the blood ammonium nitrogen concentrations increased further in three patients in whom this measurement was made.

These data, if considered in the light of other observations, are consistent with the hypothesis that increased quantities of circulating blood urea may lead to elevated arterial blood NH_4-N concentrations in patients with sufficiently abnormal hepatic function or portal circulations. Azotemia, by indirectly increasing the portal ammonium load, is an additional factor capable of precipitating or aggravating hepatic coma in some patients with cirrhosis of the liver.

Mrs. Helen Grodeck provided technical assistance.

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The Indeterminate Pulmonary Infiltration—Our Diagnostic Dilemma

Report of Twenty-Three Cases of Chronic Granulomatous Disease of the Lung

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The accurate diagnosis of the indeterminate pulmonary infiltration remains a difficult clinical and pathological problem. The increased use of pulmonary biopsy and resection has, in many instances, led to the correct diagnosis. However, in many other clinically similar cases, the exact diagnosis sill remains obscure even after biopsy. The purpose of this report is to analyze 23 cases of granuloma of the lung that presented as indeterminate pulmonary infiltrations. It is hoped that this analysis will demonstrate the similar clinical pattern of the various fungus and granulomatous diseases of the lung, the variability of laboratory aids, the important role that surgery plays in both a positive and a negative sense, and the increasing need for finer and more accurate methods of diagnosis. By its very nature, this paper is also a further plea to clinicians to exhaust all available diagnostic methods, including surgery, before committing any given patient to a long program of treatment such as that required for tuberculosis. In many of the present cases the etiology was established only by an aggressive surgical approach.

Method of Selection

The 23 cases of chronic granuloma of the lung were chosen primarily for their teaching value and the interest that they created for the staff of the pulmonary medical department rather than for their statistical significance. Twenty-one of the twenty-three cases had had thoracotomy and biopsy; the remaining two cases, both histoplasmosis, were included because of strong supporting clinical evidence for their etiology. Cases of proven tuberculosis were excluded from the study.

Some of the cases were treated initially as tuberculosis with chemotherapy, and it was only after the diagnosis was questioned, or at resectional surgery at a later date, that the real diagnosis became clear. Others were operated upon early in the course of their illness for diagnostic purposes. In the remainder, the diagnosis even after surgery was not evident.

Methods

Unfortunately, early in the study not all of the cases had complete skin tests and complement-fixation tests for fungi performed. As unusual cases were found at biopsy, however, these tests became more and more a routine procedure. Suspensions of yeast phase of Histoplasma capsulatum and extracts of yeast phase of Blastomyces dermatitidis and Coccidioides immitis were used as antigens for the complement-fixation studies. Skin tests were performed by the intradermal injection of 0.1 ml. each of 1:100 dilution of coccidioidin, histoplasmin, and blastomycin and 0.1 ml. of tuberculin purified protein derivative, 0.00002 mg. and 0.005 mg., as indicated. A skin test was interpreted as positive if an area of induration exceeded 5 mm. in diameter as read in 48 hours.

Bronchoscopies were routinely employed, and smears and cultures for fungi and tubercle bacilli were taken. Every patient had a minimum of three sputum or gastric-washing cultures for fungi and Mycobacterium tuberculosis besides the bronchoscopy specimen. One specimen was taken monthly for culture thereafter. Sputum and gastric washings were routinely studied by direct smear and by culture on Lowenstein-Jensen medium for tubercle bacilli and on brain-heart infusion agar and Sabouraud's dextrose agar for fungi. Appropriate

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TABLE 1.—*Roentgenographic Data Summary (Twenty-Three Cases)*

X-Ray Appearance	Cases	
"Nodular" Infiltration		10
Histoplasmosis	4	
Granuloma	3	
Coccidioidomycosis	1	
Blastomycosis	1	
Cryptococcosis	1	
Nodular infiltration with central cavitation		3
Cryptococcosis	1	
Mycelia-forming fungus disease	1	
Blastomycosis	1	
"Coin" lesions		6
Histoplasmosis	4	
Granuloma	1	
Coccidioidomycosis	1	
"Pneumonic" infiltration		3
Histoplasmosis	2	
Granuloma	1	
Hilar adenopathy: histoplasmosis		2
Pleural effusion: histoplasmosis		1
Hilar infiltration: histoplasmosis		1

animal inoculations were carried out in the cases with positive cultures.

Portions of resected tissues were ground with sand after direct smears of purulent or caseous material had been made. The ground tissue was diluted with sterile saline and divided into three parts. One part was used for mouse and guinea pig inoculations. The second portion was planted on three tubes of brain-heart infusion agar and two tubes of Sabouraud's medium. The remainder was digested for 24 hours at 37 C with 23% trisodium phosphate and then inoculated onto four tubes of Lowenstein-Jensen medium. The unground portion of the specimen was sectioned and stained with hematoxylin and eosin, Gridley fungus stain, and a modification of the Fite acid-fast stain.

Analysis

Of the 23 cases analyzed, 11 were found to be histoplasmosis; 5, chronic granulomas of unknown etiology; 2 each, blastomycosis, coccidioidomycosis, and cryptococcosis, and 1 case showed an unidentified mycelia-forming fungus.

Roentgenographic Appearance (Table 1).—Thirteen of the twenty-three cases were classified as having a "nodular" type of infiltration, three showing, in addition, central areas of cavitation. Six of these cases were labeled as true "coin" lesions; one had a regressive exudative and pneumonic type infiltration, and only three, all histoplasmosis, showed a varying and progressive x-ray appearance. Of these three cases, one had a migrating pneumonia; one showed bilateral basilar pneumonia with a left pleural effusion, left hilar adenopathy, and eventually a nodular infiltration in the right lower lobe, and the third case had a left hilar infiltration with hilar adenopathy.

Mycology (Table 2).—Positive tissue cultures were obtained from one case of blastomycosis, both cases of coccidioidomycosis, and one case of cryptococcosis. One case of histoplasmosis not operated upon had a positive sputum culture, and one had a positive mouse inoculation from pulmonary tissue removed at surgery. This case had a negative tissue section, however.

Both cases of blastomycosis and one case of coccidioidomycosis showed organisms in the tissue sections. Both cases of cryptococcosis also showed organisms in the Gridley fungus stains, as did eight cases of histoplasmosis. The tissue sections in the case of fungus disease of unknown etiology showed only mycelial elements. Cultures from this case were negative.

Skin Tests (Table 3).—Both cases of blastomycosis had negative skin tests with the blastomycin skin antigen. However, the 2 cases of coccidioidomycosis both had positive skin tests to the coccidioidin antigen, and 9 of the 11 cases of histoplasmosis had positive skin tests to the histoplasmin skin antigen. Four of the five cases of unidentified pulmonary granuloma had positive histoplasmin skin tests, three having positive reactions to tuberculin as well. The case of

TABLE 2.—*Mycologic Findings*

Disease Entity	Positive Tissue Sections	Positive Cultures
Histoplasmosis (11 cases)	8	2 (1 sputum; 1 mouse inoculation from tissue)
Blastomycosis (2 cases)	2	1 (tissue)
Coccidioidomycosis (2 cases)	1	2 (tissue)
Cryptococcosis (2 cases)	2	1 (tissue)
Unidentified mycelia-forming fungus (1 case)	1	0

TABLE 3.—*Skin Test Summary*

Disease Entity	Positive Tests, No.	
Histoplasmosis (11 cases)	Histoplasmin	9
	Tuberculin	8
	Coccidioidin	0
Blastomycosis (2 cases)	Blastomycin	0
	Histoplasmin	0
	Tuberculin	2
	Coccidioidin	0
Coccidioidomycosis (2 cases)	Coccidioidin	2
	Histoplasmin	1
	Tuberculin	0
Cryptococcosis (2 cases)	Tuberculin	2
	Rest negative	
Unidentified mycelia-forming fungus (1 case)	Tuberculin	1
	Only skin test reported	

fungus disease of unknown etiology had only a positive tuberculin reaction reported.

Complement-Fixation Studies (Table 4).—Six of the eleven cases of histoplasmosis had complement-fixation studies performed. Four of the six had titers of 1:16 or greater for H. capsulatum, one case having a titer that reached 1:512 and another, 1:128. One case with a small nodular infiltration had a titer of 1:16, and the fourth case showed a titer of 1:32. Three of the above cases had titers of 1:16 or greater for B. dermatitidis. The fifth case of histoplasmosis had a titer of 1:8 for B. dermatitidis alone. The sixth case showed a negative titer.

One case of coccidioidomycosis had a 1:32 complement-fixation titer for H. capsulatum; in the other case this test was not performed. The rest of the complement-fixation tests performed (one case of blastomycosis and two cases of granuloma) were negative.

Symptomatology and Geographic Data.—A detailed analysis of symptoms was not made. Twelve of the twenty-three cases had one or more pulmonary symptoms, and eleven were asymptomatic, with discovery of the pulmonary infiltration on a routine x-ray examination.

Geographic data were of indirect benefit in the evaluation of some of the cases. Both patients with coccidioidomycosis, for example, had resided in Texas, and 7 of the 11 patients with histoplasmosis had been in Panama or the Mississippi Valley. The geographic data in three cases of undifferentiated pulmonary granuloma seemed particularly significant, one patient coming from Panama and two coming from the Mississippi Valley. However, confirming bacteriologic data were not obtained.

Bronchoscopy.—Twenty-two of the twenty-three cases had negative bronchoscopies. One case of progressive histoplasmosis by x-ray showed edema and exudate of the left main-stem bronchus. The bronchial washings, however, were negative on smear and culture, although this patient had a positive sputum culture for H. capsulatum.

Comment

A review of the clinical and laboratory data of these 23 cases points up several interesting findings. Of particular importance is the lack of a "characteristic" roentgenographic picture to distinguish the fungus diseases of the lung from other granulomas, such as tuberculosis, or from neoplasm.

TABLE 4.—*Complement-Fixation Studies (Ten Cases)*

Case	Disease	X-Ray Appearance	Histoplasmosis	Blastomycosis	Coccidioidomycosis
1	Histoplasmosis	Hilar infiltration & adenopathy	1:128-1:512	1:32-1:64	Negative
2	Histoplasmosis	Migrating pneumonia, RUL, LUL	1:128	1:4 -1:28	Negative
3	Histoplasmosis	Bilateral pneumonia, left pleural effusion, hilar adenopathy, nodule RLL	1:8 -1:32	1:8 -1:16	Negative
4	Histoplasmosis	Nodular infiltration, RUL	1:16	Negative	Negative
5	Histoplasmosis	Nodular infiltration, RUL	Negative	1:4 -1:8	Negative
6	Histoplasmosis	Coin lesion, LLL	Negative	Negative	Negative
7	Blastomycosis	Nodular infiltration, RLL, with central cavitation	Negative	Negative	Negative
8	Coccidioidomycosis	Coin lesion, LUL	1:32	Negative	Negative
9	Granuloma	Pneumonic RUL	Negative	Negative	Negative
10	Granuloma	Nodular infiltration, RUL	Negative	Negative	Negative

This fact is well known. Yet, 11 of the 23 cases were considered initially as having the clinical and radiographic picture of pulmonary tuberculosis and were treated for a varied number of months with antituberculous drugs. One patient had 15 months of hospitalization with long-term antituberculous drug therapy, despite 23 negative smears and cultures for tuberculosis and negative smears and cultures from the removed surgical specimen. Another patient had eight months of antituberculous treatment before surgery. The final pathological diagnosis in both cases was "pulmonary granuloma of unknown etiology." The two cases of cryptococcosis were treated for 8 and 10 months, respectively, as tuberculosis. It could be argued that the two cases of "granuloma" represented complete sterilization of a pulmonary tuberculous lesion with drug therapy. It is our feeling now, however, that without definite proof of etiology the problem should be resolved in favor of the patient, with early surgery and shortened hospitalization. This premise is strengthened by the increasing number of reports coming from tuberculosis sanatoria of chronic histoplasmosis among hospitalized patients.[1] These reports emphasize the close simulation by histoplasmosis of tuberculosis clinically and radiographically, particularly in the chronic cavitary form. It is evident from this study that this similarity can be carried to the other pulmonary fungus entities. The number of diseases found masquerading under similar x-ray disguise is, indeed, most illuminating. Without an aggressive surgical approach this information could not have been obtained.

Two patients with the most advanced and progressive histoplasmosis by x-ray had positive H. capsulatum cultures, one from the sputum and one a positive mouse inoculation from tissue removed at surgery. The low incidence of positive cultures in the 11 cases of histoplasmosis is not surprising when it is realized that 8 of the 11 cases had localized chronic histoplasmosis. In their excellent review of histoplasmosis, Silverman, Schwarz, Lahey, and Carson[2] point out that making a diagnosis of histoplasmosis from tissue sections alone is hazardous. The only acceptable criterion for a positive diagnosis of histoplasmosis, in their opinion, is that of a positive culture. In the eight cases in the present study in which a diagnosis of histoplasmosis was based on morphologic evidence alone, strict criteria were imposed to rule out Gridley-positive artifacts, such as bits of elastic fibers and calcospherites.

In analyzing the mycologic data, the discrepancies between positive cultures and positive tissue sections in the same case further emphasize our deficiencies in these methods of diagnosis.

The skin tests are important adjuncts in the differential diagnosis of the indeterminate pulmonary infiltration. However, 4 of our 18 cases of fungus disease of the lungs (two blastomycosis and two histoplasmosis) were found to have negative skin tests. Negative skin tests in the face of active but not overwhelming fungus infection is unusual but, as demonstrated here, does not rule out with certainty the fungus disease in question.

The two cases having positive cultures for H. capsulatum and showing progressive pulmonary disease by x-ray showed complement-fixation titers of 1:128 and 1:32, respectively. A third case with a changing x-ray and hilar infiltration and adenopathy showed the highest H. capsulatum complement-fixation titer, 1:512. This high serologic level, together with the clinical picture and positive skin test, was considered by the staff to be diagnostic of histoplasmosis. Another case showing a 1:16 titer for H. capsulatum had a small nodular pulmonary infiltration, shown by x-ray. Thus, small lesions are capable of showing at least this titer elevation.

Of practical interest is the finding of cross reaction in the complement-fixation test between B. dermatitidis and H. capsulatum. This has been pointed out by Campbell and Binkley.[3] Three of the six cases of histoplasmosis tested had titers for B. dermatitidis of 1:16 or greater, and one

case had a 1:8 titer for B. dermatitidis alone, with no complement-fixation titer for H. capsulatum. The case of culturally proven coccidioidomycosis that had a 1:32 titer for H. capsulatum is unexplained, as cross reaction in the complement-fixation reaction between these two fungi usually does not occur.

Sutliff and Campbell [4] point out that there is no set level of titer that can be categorically called "significant" of infection. In a review of 192 cases of tuberculosis, they found 7.3% to have complement-fixation titers for H. capsulatum of 1:16 or greater and yet they could find no clinical or pathological evidence of histoplasmosis. It was not known if these represented false-positive reactions, cross reactions, or histoplasmosis that could not be confirmed. It was their conclusion that a positive serologic test for H. capsulatum is not adequate evidence on which to base a diagnosis unless confirmed by other clinical or mycologic data. Similarly, they point out that the serologic tests may be negative in chronic proven histoplasmosis. Thus, with the limitations of our laboratory tests, it is obvious that they can be used only as one avenue of approach toward the diagnosis of pulmonary fungus disease.

Summary and Conclusions

Twenty-three cases of fungus and other granulomatous diseases of the lung are reviewed.

The indeterminate pulmonary infiltration remains in many instances a difficult diagnostic problem to the clinician and to the pathologist.

Skin tests, serologic data, cultures and smears, examination of biopsy material, geographic data, and bronchoscopy are all valuable adjuncts in the diagnosis of the indeterminate pulmonary lesion. However, deficiencies and pitfalls with these aids are enumerated and stressed.

Emphasis is placed on the similarity of the chest roentgenograms of the various fungus and other granulomatous diseases of the lung. Every effort, including thoracotomy and biopsy, should be made to establish a diagnosis before calling a given lesion tuberculous and committing the patient to long-term antituberculous therapy.

Pulmonary biopsy, although our most valuable aid, also has limiting factors from the pathologic and cultural standpoints.

An aggressive surgical approach and better histopathologic, cultural, and serologic methods are all greatly needed in our quest for an accurate diagnosis of the indeterminate pulmonary infiltrations.

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The Post-Myocardial-Infarction Syndrome

A Report on Forty-Four Cases

WILLIAM DRESSLER, M.D., New York

A complication of acute myocardial infarction, which mimics the postcommissurotomy syndrome and idiopathic pericarditis, has been described.[1-3] The clinical features are fever; chest pain; evidence of pericarditis, pleurisy, and pneumonitis, and a tendency to recurrences. Several reports have corroborated these observations.[4-6] The complication was previously often mistaken for recurrent myocardial or pulmonary infarction.

After the preliminary report, a larger number of patients who presented the post-myocardial-infarction syndrome has been observed. One of the patients who was treated with anticoagulants in the presence of diffuse pleuropericarditis died of cardiac tamponade. It is the purpose of the present communication to report additional information obtained in the past two years and to stress the danger of anticoagulant therapy in the presence of the post-myocardial-infarction syndrome.

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This report includes 13 cases which were reported previously.[2,3]

From the Department of Medicine of the Maimonides Hospital and the State University of New York College of Medicine at New York City, Brooklyn.

Report of Cases

CASE 1.—A 62-year-old man who had diabetes was admitted to the Maimonides Hospital on Nov. 20, 1955. On the morning of the day of admission he was seized with severe precordial pain which radiated to the left arm and persisted for nine hours.

Physical examination revealed a rectal temperature of 98.6 F, a blood pressure of 140/90 mm. Hg, and a heart rate of 72 per minute. There was no evidence of congestive heart failure. The lungs were clear. The apex beat of the heart was not palpable. The cardiac dullness was not enlarged. The heart sounds were of fair quality, and the rhythm was regular. No murmurs were audible. The liver and spleen were not palpable.

Laboratory Findings.—Hemoglobin was 12.1 gm. per 100 ml.; leukocytes, 7,550 per cubic millimeter, with 86% neutrophils; sedimentation rate, 36 mm. in one hour (Wintrobe); fasting blood sugar, 137 mg. %; urea nitrogen, 22 mg. %, and urine, many pus cells but no erythrocytes. Culture of the urine revealed Escherichia coli. An electrocardiogram taken a day after the acute episode

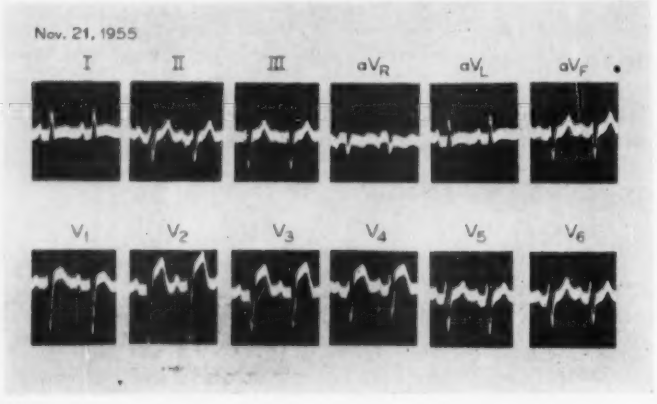


Fig. 1 (Case 1).—Signs of recent antero-septal-wall myocardial infarction.

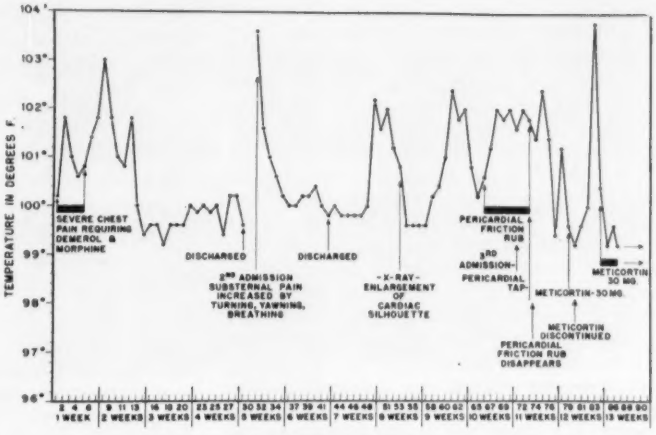


Fig 2 (Case 1).—The temperature chart covers 13 weeks following the coronary attack, during which the patient suffered four flare-ups of fever; the last prolonged febrile period was terminated by administration of prednisone (Meticorten).

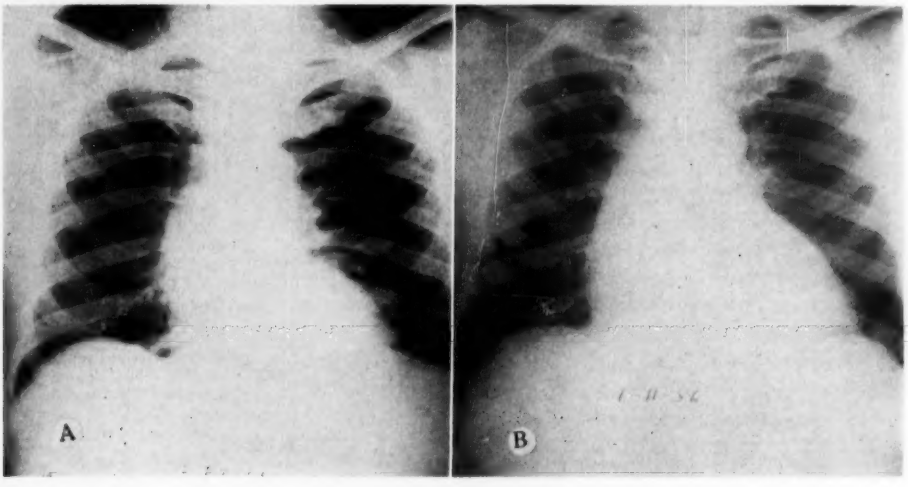
showed signs indicative of acute antero-septal-wall myocardial infarction (Fig. 1).

Course.—During the first five days of illness the patient complained of severe sticking chest pain, which required meperidine (Demerol) for relief. The possibility of extension of the infarction was considered, but serial electrocardiograms failed to support this view. The rectal temperature (Fig. 2) rose to 101.8 F on the second day and reached another peak of 103 F on the eighth day of illness. It did not return to normal until two weeks after the initial attack. In the fourth week the temperature rose again to 100 F and slightly above. This was thought to be due to urinary infection as a result of insertion of a Foley catheter.

The patient was treated with bishydroxycoumarin (Dicumarol) from the 1st to the 22d day of illness. The longest prothrombin time, 37 seconds, was observed on the ninth day. Otherwise, during the whole course of anticoagulant therapy, the prothrombin time ranged from 18 to 31 seconds. There were no hemorrhagic complications.

The patient was discharged on the 30th day of illness. He was readmitted on the following day, when he developed an attack of severe substernal pain which was aggravated by breathing, yawning, and turning in bed. His temperature (Fig. 2) rose to 103.6 F and fell gradually, without reaching normal levels in the subsequent two weeks. The electrocardiogram did not show additional changes.

Fig. 3 (Case 1).—*A*, six weeks after the coronary attack, there was no evidence of pericardial effusion. *B*, in the eighth week, significant enlargement of the cardiac silhouette suggested pericardial effusion.



Pericarditis was strongly suspected, but there was no pericardial friction rub, nor did x-ray study (Fig. 3*A*) support a diagnosis of pericardial effusion. The sedimentation rate was 26 mm. in one hour. The patient was discharged six weeks after the onset of myocardial infarction.

In the following week the temperature rose again to 102.2 F and remained elevated for six days. From time to time the patient felt stabbing pain in the chest, which lasted for a few minutes. In the eighth week, x-ray study of the chest (Fig. 3*B*) indicated increase of the cardiac silhouette. There was a new rise in temperature, which persisted for three weeks. Signs of urinary infection were no longer present, and antibiotics failed to influence the fever.

A pericardial friction rub was heard for the first time on the 66th day of illness; it remained audible for 8 days. The patient was admitted to the hospital for the third time on Jan. 29, 1956. Pericardial paracentesis was done on the 73d day of illness. A straw-colored fluid which rapidly coagulated was obtained. It contained 4.7 gm. % protein, many red blood cells, and leukocytes. Cultures of the aspiration fluid, as well as of blood, yielded no growth.

Since the febrile condition persisted, administration of prednisone (Meticorten) was started on the 79th day; 30 mg. was given on each of 2 days. When the temperature fell promptly prednisone was temporarily withdrawn to ascertain whether or not cessation of fever was concidental. However, there was a new steep rise of temperature up to 103.6 F (Fig. 2). Therefore, administration of prednisone was resumed, and the temperature returned quickly to normal. Improvement persisted while the dosage of prednisone was gradually reduced, and the patient was discharged 87 days after onset of the illness. When prednisone was withdrawn after six weeks there was no relapse.

Summary.—Acute myocardial infarction was followed by a prolonged period of fever and chest pain. Relapses of fever and pain occurred in the fifth, seventh, and ninth weeks of illness. Enlargement of the cardiac silhouette suggesting pericardial effusion was noted eight weeks after the coronary attack. A pericardial friction rub was heard for the first time in the 10th week of illness. Pericardial paracentesis produced a straw-colored fluid which had the characteristics of an exudate. Fever and chest pain were promptly terminated by use of prednisone. The illness lasted for more than three months.

CASE 2.—A 54-year-old physician was admitted to the Maimonides Hospital on June 10, 1956. He gave a history of allergic reactions to spicy foods and various drugs, including penicillin. A day prior to admission he experienced for the first time squeezing substernal pain of short duration associated with effort. On the following day similar attacks occurred even when the patient rested. On June 12, chest pain was excruciating and lasted for several hours.

Physical Examination.—Rectal temperature, 102.4 F (Fig. 4); blood pressure, 114/80 mm. Hg, and heart rate, 100 per minute. There was neither tenderness of the calves nor signs of congestive heart failure. The lungs were clear. The apex beat of the heart was not palpable. The area of cardiac dullness was not enlarged. There was exquisite tenderness to percussion over the precordium. The heart sounds were distant. The liver was not palpable.

Laboratory Findings.—Urine was normal; hemoglobin, 14.8 gm. per 100 ml.; leukocytes, 8,000 per cubic millimeter, with 67% neutrophils; sedimentation rate, 5 mm. in one hour. (Wintrobe), and fasting blood sugar, 96 mg. %. An electrocardiogram, taken on June 11, 1956, showed flat T-waves in Leads V_5 and V_6. Another tracing, taken a day after the severe attack of pain (Fig. 5),

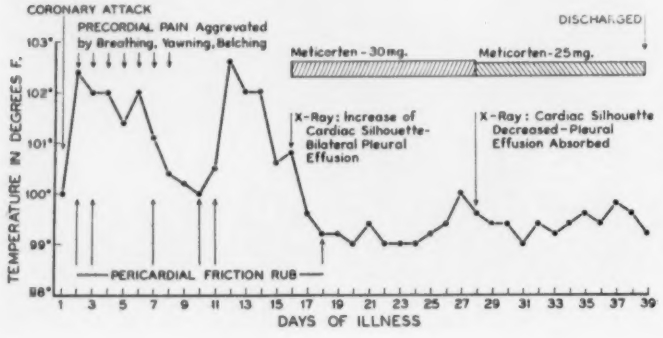


Fig. 4 (Case 2).—The initial fever forms a plateau curve which is unusually high and somewhat prolonged; a second flare-up is indicated by rise in temperature on the 11th day of illness. Prednisone (Meticorten) given on the 16th day caused a prompt drop in temperature.

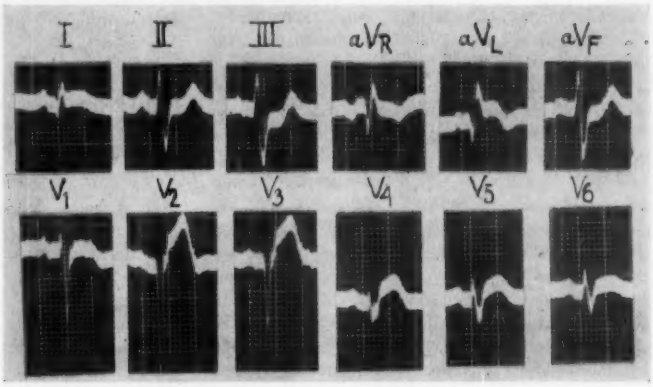


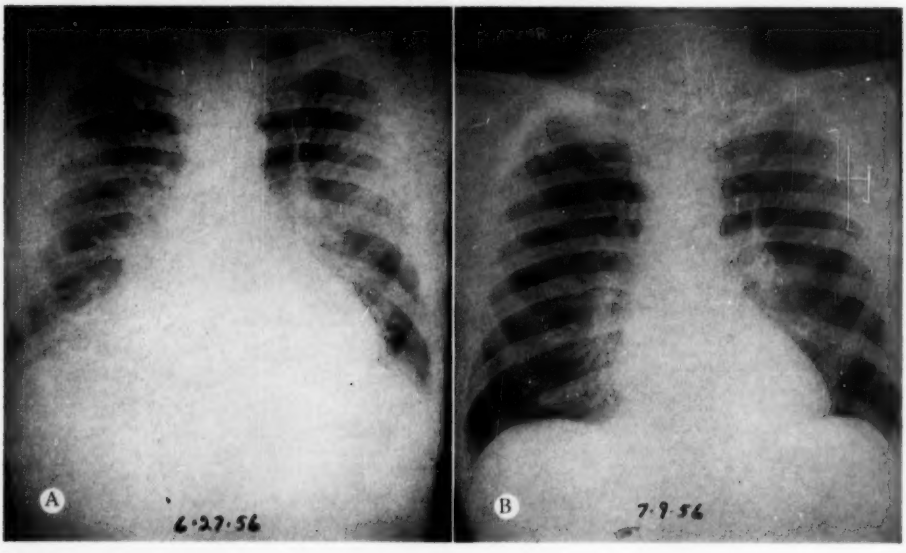
Fig. 5 (Case 2).—Signs of recent anteroseptal-wall myocardial infarction.

showed Q-S deflections in the Leads V_2 and V_3 and elevation of ST in V_2 through V_6, indicative of acute anteroseptal wall infarction.

Course.—On the morning of June 13, the day after the severe coronary attack, the patient complained of a new type of chest pain, which he described as "searing" and which was felt in the precordial region, distinctly aggravated by deep inspiration, yawning, twisting of the body, and belching. For four successive days the pain was severe enough to require injections of analgesics in addition to acetylsalicylic acid. Then its severity decreased, and a slight discomfort, described as "pulling sensation," was felt only with taking a deep breath or yawning. Simultaneously with the onset of pleuropericardial pain a pericardial friction rub appeared, which was audible for 2 days; it was heard again on the 7th, 10th, and 11th days of illness. The fever curve (Fig. 4), after forming a plateau with peaks of 102 F for 5 days, dropped to 100 on the 10th day of illness.

On the 11th day after the episode of severe "coronary" pain the patient complained of feeling a lump in the epigastrium "like indigestion." On the next day the temperature rose to 102.8 F. A leukocytosis of 17,000 per cubic millimeter with 78% neutrophils was noted. X-ray study on June 27 (Fig. 6*A*) revealed enlargement of the cardiac silhouette to the right and left, with widening of the waist, consistent with pericardial effusion. The

Fig. 6 (Case 2).—*A*, 15 days after the coronary attack, the cardiac silhouette is enlarged and its waist widened. Pulmonary vascular markings are accentuated. *B*, 12 days after the first x-ray study, the size of the cardiac silhouette is distinctly reduced.



pulmonary vascular markings were accentuated. Examination in the oblique views revealed bilateral posterior costophrenic effusions.

The second bout of fever, after lasting for six days, was abruptly terminated by administration of prednisone, which was given in a daily dose of 30 mg. The temperature remained normal thereafter. A pericardial friction rub was heard again on the 18th day of illness. Progressive improvement was indicated by serial x-ray studies. On July 9, 1956 (Fig. 6*B*), the heart and lungs appeared essentially normal except for slight prominence of the left lower contour.

The patient was discharged on July 20, 1956, 39 days after the severe coronary attack. He continued taking prednisone in decreasing dosage for a total of six weeks. There was no ill effect after withdrawal of the drug.

Bishydroxycoumarin was given for the first nine days of illness. It was discontinued when signs of complicating pericarditis became manifest. The longest prothrombin time observed was 30 seconds. There were no hemorrhagic complications.

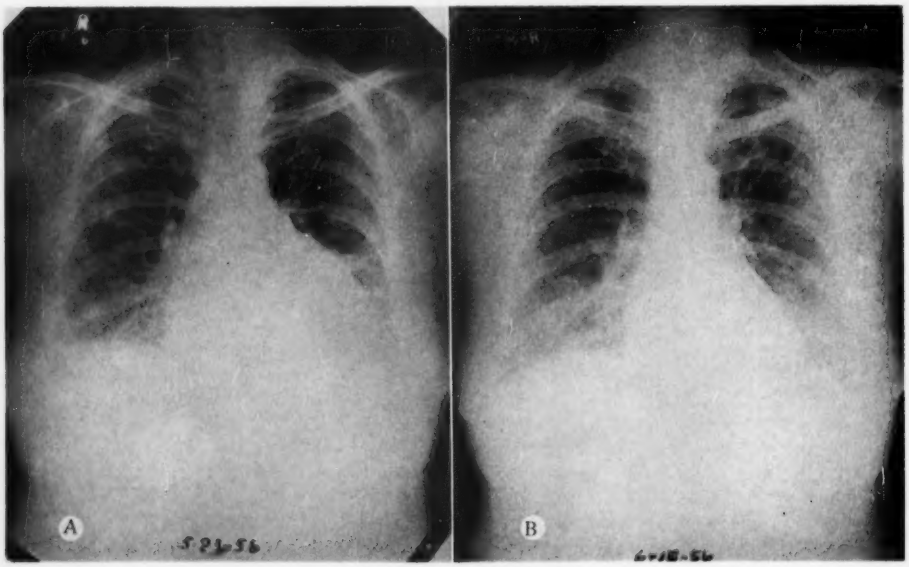
Summary.—Evidence of pericarditis was manifest one day after onset of a myocardial infarction. A pericardial friction rub was heard on and off from the 2d to the 11th day of illness and again on the 18th day. The initial febrile period lasted for 10 days. A second bout of fever, associated with epigastric pain, developed on the 11th day of illness. X-ray study indicated pericardial and pleural effusions. Administration of prednisone caused rapid and lasting improvement. The illness lasted for six weeks.

Case 3.—A 56-year-old woman, who suffered from diabetes, complained for the first time of pain across the chest while shoveling snow in the first half of March, 1956. The chest distress subsided when the patient rested but returned promptly when she made another attempt at shoveling snow. The second time the pain persisted somewhat after the patient had discontinued the unaccustomed work.

About six weeks after that attack, which was by then completely forgotten, the patient developed fever and a tightening sensation in the neck, jaw, and substernal region. The discomfort, unlike that of the previous attack, was aggravated by drawing a deep breath and turning in bed. After four days' duration pain and fever ceased but recurred on May 8, 1956.

The patient was hospitalized, in Newark, N. J., on May 12, 1956. An electrocardiogram taken there showed inversion of the T-waves in the precordial leads and signs suggestive of old posterior-wall infarction, the latter being obviously related to the transient pain which the patient had experienced six weeks previously. The temperature was ele-

Fig. 7 (Case 3).—*A*, May 23, 1956, the cardiac silhouette is enlarged. There are patches of infiltration in both pulmonary bases and signs suggestive of bilateral pleural effusion. *B*, June 15, 1956, the size of the cardiac silhouette has returned to normal.



vated, with peaks of 104 F for 17 days. On May 16, 1956, the pain shifted to the left shoulder and arm.

Serial x-ray studies revealed progressive enlargement of the cardiac silhouette. A 6 ft. film, taken on May 23, 1956 (Fig. 7*A*), showed a large cardiac silhouette, patches of infiltration in both pulmonary bases, and changes suggestive of bilateral pleural effusion. The nature of the condition was not clear. Antibiotics had no effect. At one time thyroiditis was suspected, and propylthiouracil was given. A cardiac consultant suggested that extension of myocardial infarction had occurred and advised use of anticoagulant therapy. On the 18th hospital day a pericardial friction rub became audible and anticlotting therapy was discontinued, after five days' duration. The prothrombin time was never higher than 19 seconds. On May 29, 1956, the temperature dropped and x-ray study showed reduction in the size of the cardiac silhouette.

On May 31, 1956, the patient was transferred to the Maimonides Hospital. Physical examination revealed a rectal temperature of 100 F, blood pressure of 96/64 mm. Hg, and a heart rate of 90 per minute. Xanthelasma was noticed at the left lower lid. There was no pitting edema of the legs. The breath sounds were diminished over both pulmonary bases. The cardiac dullness was increased to percussion. A pericardial friction rub was audible. The heart sounds were distant. The cervical veins were not engorged. The liver was not palpable. There was no calf tenderness.

Laboratory Findings.—Urine was negative; hemoglobin, 13.2 gm. per 100 ml.; leukocytes, 7,400 per cubic millimeter, with 50% neutrophils and 5% to 6% eosinophils in repeated counts; fasting blood sugar, 159 mg. %; serum cholesterol, 341 mg. %; L. E. preparation, negative; antistreptolysin titer, less than 100 units; heterophil agglutination test, 1:10 positive; repeated blood cultures, negative; C-reactive protein, 2+, and sedimentation rate (Wintrobe), 47 mm. in one hour.

Serial electrocardiograms showed significant Q-waves and inverted T-waves in Leads II, III, and aV_F and inversion of T-waves in the precordial leads. The latter changes were attributed to pericarditis. X-ray studies, on June 5, 1956, revealed peribronchial infiltration in both pulmonary bases. On June 15 (Fig. 7*B*) the size of the heart silhouette had regressed to normal.

Course.—The pericardial friction rub disappeared on the third hospital day. The patient complained on and off about pain in the sternal region and left shoulder, aggravated by breathing, during four weeks of hospitalization; slight rises in temperature above 100 F were occasionally recorded. Multiple indolent nodes of slightly more than pea size developed in the subcutaneous tissue of the fingers, lasting for several weeks. Eosinophilia persisted.

The patient was discharged on July 7, 1956. The final diagnosis was diabetes, coronary arteriosclerosis, posterior-wall myocardial infarction (old), and pericarditis, pleurisy, and pneumonitis (post-myocardial-infarction syndrome).

Summary.—An acute coronary attack, resulting in a posterior-wall ischemic lesion, manifested itself merely by transient mild anginal pain and remained unrecognized. Six weeks later, recurrent bouts of fever and chest pain of pleuropericardial type developed. About two months after the coronary attack, a pericardial friction rub was heard and serial x-ray studies revealed signs of pericardial and pleural effusions and of pulmonary infiltration. The patient was not treated with anticoagulants prior to the development of the complication. The latter lasted for about two months.

CASE 4.—A 57-year-old man was admitted to the Maimonides Hospital on June 13, 1957. Two days prior to admission he began to complain of "chest oppression." On June 12, the attacks of chest distress became severe and prolonged and were associated with convulsions. Physical examination revealed a rectal temperature of 102.4 F, blood pressure of 108/70 mm. Hg, and heart rate of 108 per minute. There was no evidence of congestive heart failure. The lungs were clear. The cardiac apex beat was not palpable. The heart was not enlarged to percussion. The heart sounds were of good quality. No pericardial friction rub was heard. Liver and spleen were not palpable.

Laboratory Findings.—Urine was negative; leukocytes, 18,000 per cubic millimeter, with 76% neutrophils; hemoglobin, 14.0 gm.; sedimentation rate, 25 mm. in one hour (Wintrobe); fasting blood sugar, 123 mg. %; urea nitrogen, 15 mg. %; serum cholesterol, 280 mg. %, and serum glutamic oxalacetic transaminase, 220 units. An electrocardiogram taken on the day of admission showed Q-S deflections and marked elevation of ST in all precordial leads, indicative of extensive anterior-wall myocardial infarction.

Course.—During the first three days after the severe coronary attack, the patient continued to complain about pain in the left side of the chest and back associated with "difficulty in breathing." A bedside x-ray study (Fig. 8*A*) was made on the fourth day of illness. It revealed homogeneous haziness at the left side of the chest, which was interpreted as due to pleural effusion. On the third day the temperature dropped from 102 F to

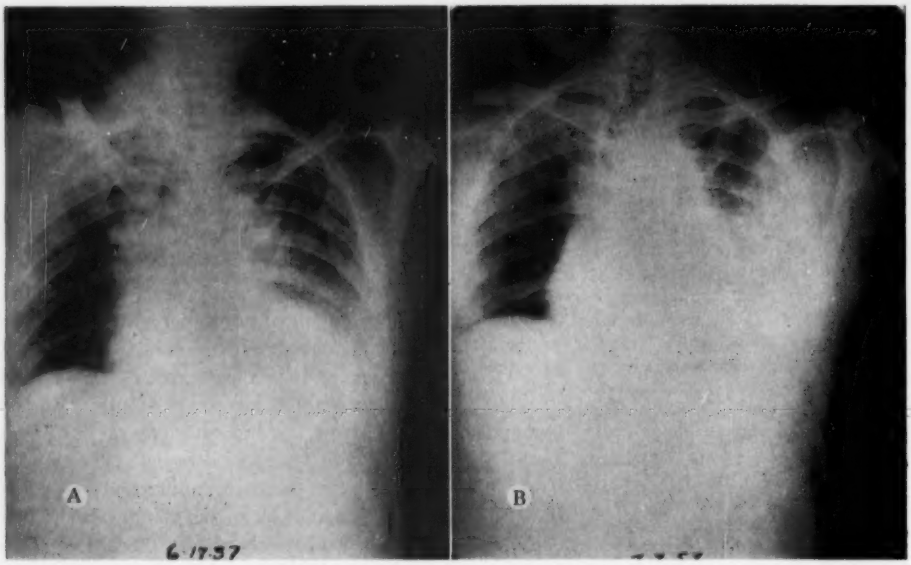


Fig. 8 (Case 4).—*A*, (bedside examination) on the third day after the coronary attack, there is evidence of left-sided pleural effusion. *B*, (bedside study, day of death) 23 days after *A*, left-sided pleural effusion has increased. Straightening of the upper half of the left border of the heart silhouette is compatible with pericardial effusion.

100.2 F, and for eighth days it continued at a level close to 100 F. The temperature was normal on the 12th and 13th days of illness.

On June 26 (the 13th day), the patient complained of severe pain in the midchest and left shoulder, which was aggravated by breathing. On the following day the temperature rose to 101 F and mild substernal pain was felt when the patient took a deep breath. A tentative diagnosis of pleuropericarditis was made. The temperature dropped to 100 F on June 28, 1957. A pericardial friction rub was first heard on July 1, the 18th day of illness, and remained audible for three days. The patient was then comfortable and felt only occasionally a tightening along the sternum when asked to take a deep breath. The white blood cell count at that time was 10,800 per cubic millimeter with 81% neutrophils.

Administration of bishydroxycoumarin was started on the day of the severe coronary attack. The prothrombin time was kept well within therapeutic range. During the first three weeks it was 30 seconds only once, and it remained below this level on all other days. Anticoagulant therapy was erroneously continued after the complication of pericarditis was diagnosed. Until July 6, frequent microscopic studies of the urine failed to show red blood cells; nor was there evidence of other hemorrhagic complications.

On July 5, the prothrombin time rose to 39 seconds; on the next day it was 33 seconds. However, "many red blood cells" appeared in the urine on that day. Anticoagulant therapy was then discontinued. The patient's condition gradually deteriorated. The temperature rose to 101 F on July 5 and to 102 F on July 7. X-ray studies on July 5 revealed an increase in the amount of fluid in the left pleural cavity; also, the possibility of pericardial effusion was mentioned.

On the morning of July 8, the heart rate was 128 and gallop rhythm was noted. The pulse was barely palpable. Percussion revealed increase of the cardiac dullness, which was thought to be due to pericardial effusion. A portable x-ray study (Fig. 8*B*) showed straightening of the left heart border, which was consistent with pericardial effusion. Also, the amount of fluid in the left pleural cavity appeared increased in comparison with previous studies. A clinical diagnosis of cardiac tamponade due to pericarditis and hemopericardium was made. Pericardial paracentesis yielded about 30 cc. of stark bloody fluid whose hematocrit was 33%, while that of the simultaneously tested venous blood was 38%. Since it proved difficult to withdraw a larger amount of pericardial fluid by aspiration and the patient's condition rapidly deteriorated, it was decided to perform pericardiotomy. During the preparations the patient died.

Postmortem Examination.—Examination revealed coronary arteriosclerosis with occlusion of the descending branch of the left coronary artery;

healing antero-septal-wall myocardial infarction of an estimated duration of three or four weeks; organizing diffuse pericarditis; hemopericardium (380 cc.); hemothorax (1,000 cc. in the left pleural cavity and 150 cc. in the right); hemoperitoneum (500 cc.); ecchymoses in the pericardium and peritoneum; atelectasis of both lungs, particularly marked in the left lower lobe, and nonspecific interstitial pneumonitis with focal pulmonary fibrosis, the inflammatory changes extending into the visceral pleura.

The myocardial infarction involved the whole thickness of the ventricular wall. It occupied the better (lower) half of the interventricular septum and all of the apical area, including the lateral and posterior portions and extending about one-quarter of the distance toward the base. The infarcted area was thinned out and dilated in aneurysmal fashion. No rupture of the myocardium or coronary branches was present.

The pericardial cavity contained besides fluid blood many blood clots. The visceral and parietal pericardium appeared shaggy, with thick fibrinous layers, and were slightly adherent in some spots. Microscopic study revealed thickening of epicardium and pericardium by marked granulation-tissue reaction with cellular infiltration, mainly composed of histiocytes, fibroblasts, and round cells. In some areas plasma cells predominated, with occasional eosinophils. Thin bands of fibrous tissue were seen within the granulation tissue.

The lungs showed no signs of infarction. All pulmonary artery branches were open. Microscopically, there were histiocytes and hemosiderin-containing macrophages, the latter in groups and masses. Occasional streaks of round-cell infiltration were noted, mainly in relation to bronchioles and blood vessels. In many sections these changes extended into the corresponding visceral pleura.

Summary.—Extensive myocardial infarction was followed by prolonged low-grade fever and pain of the pleuropericardial type. There was early roentgenologic evidence of pleural effusion. A pericardial friction rub was heard from the 18th to 20th days of illness. Anticoagulant therapy was used from the day of the coronary attack to the 23d day of illness, until the urine showed transient microscopic evidence of hemorrhage. The patient died two days later, after symptoms and signs of cardiac tamponade had made their appearance. Postmortem examination revealed extensive healing myocardial infarction, diffuse organizing pericarditis, interstitial pneumonitis and pleuritis, hemopericardium, bilateral hemothorax, and hemoperitoneum.

Comment

Forty-four patients with recent myocardial infarction whose clinical picture did not conform to the textbook pattern of myocardial infarction were studied. There were prolonged and recurrent fever and chest pain. Relapses occurred frequently and caused prolongation of the clinical course by several weeks or months. Such features are usually attributed to recurrent myocardial or pulmonary infarction. However, in the patients studied, electrocardiographic signs of extension of myocardial infarction were absent, and there were no features indicative of phlebothrombosis in the lower extremities or obvious signs of pulmonary infarction. Instead, evidence of generalized pericarditis with effusion often associated with pleurisy and pneumonitis was observed. This triad, which closely resembles the postcommissurotomy syndrome and idiopathic pericarditis, has been referred to as the post-myocardial-infarction syndrome.

Pericarditis.—Involvement of the pericardium is generally considered an insignificant feature which accompanies recent myocardial infarction when necrosis extends toward the epicardial surface [7,8] ("pericarditis epistenocardica" [9]). Its clinical manifestation is a fleeting pericardial friction rub (Table) [10] which is audible in from

Pericarditis

As Sign of Recent Myocardial Infarction	As Major Complication of Myocardial Infarction
Pericardial friction rub is usually heard between the 2nd & 4th days of illness.	Pericardial friction rub is heard between the 2nd & 11th weeks of illness.
Pericardial friction rub is evanescent.	Pericardial friction rub lasts from 3 days to 3 wk.
Pericardial effusion is extremely rare.	Pericardial effusion is common.
Pericarditis is not associated with pleurisy & pneumonitis.	Pericarditis is often accompanied by pleurisy & pneumonitis.
Pericarditis does not recur.	Recurrences are a significant feature.

10% to 30% of patients in the first few days of the illness. Pericardial effusion, however, is thought to be extremely rare.[7-10] According to Friedberg,[11] effusion is "probably overlooked in most cases in which it occurs." Friedberg does not mention any serious implication of this condition, nor does he point out pericarditis among the complications of myocardial infarction. The prevailing view on the subject of pericarditis is probably best expressed by McGuire and associates,[12] who state, "Pericarditis occurring in . . . myocardial infarction is usually an incidental finding in the course of a more important disease." In the cases of this series, however, pericarditis represents a major complication which often overshadows and outlasts the basic illness. Its clinical manifestations, besides fever and pleuropericardial pain, are a pericardial friction rub, which has certain characteristic features, and signs of pericardial effusion.

The friction rub which is significant of pericarditis as a major complication (Table) occurs late, that is, between the 2d and 11th weeks of illness; it has a tendency to persist from three days to as many weeks and to recur. Such features are occasionally mentioned in the literature as due to large myocardial infarctions.[11] However, study of the present series indicates that a pericardial friction rub which occurs late and is of long duration does not necessarily accompany extensive infarction but is invariably associated with other features, such as prolonged fever, pleuropericardial pain, and pericardial and pleural effusions, which constitute the complication referred to as post-myocardial-infarction syndrome.

Among 32 patients of this series who had adequate clinical records, 25 (78%) presented a pericardial friction rub, significant either by late incidence (in 24 patients) or by long duration (in 18 patients) or by both features combined (in 17 patients). In 7 cases the friction rub appeared in the second week of illness; in 11, in the third week, and in 12, later than the third week. In two patients the rub was heard for the first time as late as 10 weeks after the initial episode, and in one instance, in the 11th week of illness. In seven patients the friction rub recurred once or several times during a prolonged illness. The rub remained audible for a week or longer in nine patients, for 17 days in two instances, and for three weeks in one case.

Evidence of pericardial effusion, that is, first, enlargement and, then, rapid shrinking of the cardiac silhouette, was found in 62% of 34 patients in whom serial x-ray studies were available. In three cases the diagnosis was confirmed by paracentesis, which in one instance yielded straw-colored exudate, and in two patients, intensely hemorrhagic fluid. One of the latter patients had received anticoagulant therapy.

Pleuritis.—Pleuritis is not known as a feature of uncomplicated myocardial infarction. When it is present it is usually attributed to complicating pulmonary infarction. Among the patients in this series pleural effusion was a common finding in the absence of congestive heart failure, evidence of phlebothrombosis, or pulmonary infarction. Among 35 patients, in whom adequate x-ray studies were made, 68% showed signs of pleural effusion, which was unilateral in 8 and bilateral in 16 patients. The amount of pleural effusion was usually small, pericarditis being the dominant feature. In six patients, however, pleural effusion was marked, necessitating repeated paracentesis. This yielded serous exudate in one-half of the cases and intensely hemorrhagic fluid in the other half. In one instance (Case 4) anticoagulant therapy was apparently a factor in causing hemothorax on the basis of existing pleuritis.

Pneumonitis.—Pneumonitis occurred less frequently than pericarditis and pleurisy. Of 35 patients with adequate clinical and roentgenologic records, 10 (28%) showed pulmonary infiltration, either linear or in patches, mostly located in the bases of the lungs. None of these patients presented obvious evidence of pulmonary infarction or phlebothrombosis in the lower extremities. In three instances hemorrhagic expectoration developed in the first few days after

the coronary attack. One of the patients, reported elsewhere,[3] exhibited loud bronchial breathing on the third day of illness, and serial x-ray studies revealed opacification rapidly spreading over both lungs. The process was not influenced by antibiotics, while treatment with prednisone was followed by rapid improvement. Failure to respond to antibiotics and association with pericarditis and other features of the post-myocardial-infarction syndrome characterize this type of pulmonary inflammation.

Geever and associates [13] reported on postmortem findings of "atypical pulmonary inflammatory reactions" in three instances of recent myocardial infarction. The microscopic features were similar to those of atypical or rheumatic pneumonia. The authors thought that the association of this type of pneumonitis with myocardial infarction was more than coincidental. Their Case 1 presented extensive bilateral bronchopneumonia with abundant bloody sputum and generalized pericarditis. The authors raised the question of whether they were possibly dealing with a process of viral or allergic etiology. Case 4 of the present series presented at postmortem examination a triad of pericarditis, pleuritis, and interstitial bronchopneumonia, complicated by the toxic effect of anticoagulant therapy. The pneumonia did not show specific features as described by Geever and associates.

Hemorrhagic Exudate.—Intensely hemorrhagic exudate has been observed in post-myocardial infarction syndrome, as in idiopathic pericarditis and postcommissurotmy syndrome. Goldstein and Wolff [14] drew attention to the danger of pericardial bleeding and cardiac tamponade in patients with generalized pericarditis who received anticoagulant therapy. This danger must not be underestimated, as was proven by the experience with Case 4 of this series. Fortunately, cardiac tamponade is a rare event. A good number of the patients here described, whose condition was not recognized for some time, were treated with anticoagulants without ill effect, even though renal hemorrhage occasionally occurred. On the other hand, it should be borne in mind that hemorrhagic pericarditis and pleurisy may occur in the complication here described in the absence of anticoagulant effect. Hemorrhagic pneumonitis may develop in the first few days after the coronary attack, being readily mistaken for pulmonary infarction.

Fever.—As a rule fever is present, with an average range of from 101 F to 102 F; occasionally peaks of 103 F and 104 F are observed. When fever due to the complication coincides with the initial febrile period of myocardial infarction, it may cause a second peak, a plateau type of temperature curve which is higher than that of uncomplicated myocardial infarction, and prolongation of the initial febrile period. Between flare-ups of pleuropericarditis, when the process is smoldering, the temperature drops to the neighborhood of 100 F. In some patients the temperature never runs higher than 100 F in spite of the presence of pericarditis.

Pain.—Pain is the most sensitive index of complicating pleuropericarditis and often precedes the onset of fever. It is absent only in exceptional cases. When it is missing in the first attack, it may appear with the second or third flare-up. Its intensity, however, varies widely from crushing and agonizing to dull, or it may be just a raw feeling, which the patient often fails to mention unless he is specifically questioned about it and is asked to take a deep breath. The pain may last a few hours or several weeks, with varying intensity. It is described as "pressing, squeezing, tightening, like a weight, searing, sharp, stabbing, or sticking" and in mild cases as "dull, pulling, or drawing." The site of the pain may be the chest, notably the substernal area and the precordium; both sides of the neck, jaws, shoulders, and arms; the supraclavicular areas; the epigastrium, and the right hypochondrium. It can be seen that both the character and the site of the distressing sensation are largely identical with the features of a coronary attack, for which the condition is indeed mistaken by patient and

physician unless thorough questioning elicits the characteristic fact that the discomfort is aggravated by deep inspiration, turning in bed, yawning, coughing, or, in rare instances, swallowing. We have often noticed that the pain caused by deep breathing was located exactly in the area where the pericardial friction rub was audible. The substernal location of the pain, elicited or aggravated by deep inspiration, appears to be one of the most characteristic marks of pericarditis.

Laboratory Data.—Leukocytosis of from 10,000 to 20,000 per cubic millimeter, rarely in higher amounts; neutrophilia, and high sedimentation rate are present in the vast majority of cases. In contrast to the short-lasting increase of the leukocyte count in uncomplicated recent myocardial infarction, the leukocytosis of the complication persists for weeks. This and an elevated sedimentation rate suggest activity of the process even when a drop in temperature seems to indicate a return to normal. In instances with a protracted course of the complication the values for hemoglobin may drop considerably, necessitating in exceptional cases the transfusion of blood. Eosinophilia was observed in one-fifth of the cases. In two instances an increase of the transaminase values to 93 and 48 units, respectively, was noted at 15 days and at four months after the coronary attack, in the absence of signs of extension of myocardial infarction.

Cultures of blood and pericardial and pleural fluid yielded no growth. In instances of marked pneumonitis a search for a responsible bacterial agent was unsuccessful. Tuberculin skin tests were negative, as was search for acid-fast bacilli, L. E. cells, cold agglutinins, heterophil antibodies, and agglutinins for typhoid, paratyphoid, and Brucella infection.

Changes of the electrocardiogram compatible with pericarditis were observed in one-half of the patients in whom adequate electrocardiographic studies were available. Yet, the electrocardiogram proved to be of limited value for the diagnosis of pericarditis when recent myocardial infarction was present. Serial x-ray studies, in addition to thorough clinical observation, are of greatest importance in the recognition of the post-myocardial-infarction syndrome.

Course.—It is often difficult to determine the onset of the syndrome because its most striking feature, rise in temperature, may coincide with fever caused by the acute myocardial infarction. There are many indications, however, which point to early development of the complication, at least in the majority of cases. A pericardial friction rub appeared in the first week of illness in more than one-half of the patients. Similarly, pleuropericardial pain often developed in the first week, indeed, as early as a day or two after the onset of the myocardial infarction. The initial febrile period usually lasted longer than in uncomplicated myocardial infarction, namely, from 8 to 14 or more days; also, temperatures were higher, as a rule, and the onset of the complication was often marked by a second peak of fever.

Signs of severe pneumonitis appeared in a few patients on the third or fourth day of illness. Evidence of pericardial or pleural effusion, however, was infrequently noted before the beginning of the 3d week and in occasional instances not until the 10th or 11th week of illness. Thus, the impression may be gained, especially if the patient has not been seen in the early stages, that the complication developed many weeks after the coronary attack. It is possible, however, that unobtrusive signs during the early stage of the complication were overlooked.

Each episode of chest pain and fever lasts for a week or two; in exceptional instances, from three to six weeks. Recurrences are common. Only in nine patients was the illness limited to a single bout. Eighteen patients had two or three episodes, and ten patients, from four to seven bouts. Between flare-ups the temperature may be close to normal, but persistent leukocytosis

and an elevated sedimentation rate should arouse suspicion that a stage of smoldering activity exists.

The duration of the illness varies with the number of recurrences. In eight patients the complication lasted from one to two weeks, and in six instances, for more than three months. Two patients, still under observation, developed relapses as late as 10 months and 12 months, respectively, after the coronary attack. One of these patients was treated with prednisone and suffered a rebound whenever the daily dosage was reduced to less than 15 mg.

Incidence.—To gain dependable information as to the incidence of the syndrome has proved a very difficult task, even if one is able to draw on the material of a large hospital. The initial episode occurring during hospitalization often remains unrecognized unless one is particularly alert to this syndrome. A second bout may not occur until the patient has been discharged into domestic care, where the causal relationship to the basic condition is frequently overlooked. Furthermore, some of the patients observed in the hospital, where these studies were made, received adrenal steroids in an early stage, when the post-myocardial-infarction syndrome was only suspected. This therapy modified the course and made an exact diagnosis impossible.

The complication is by no means rare; indeed, it seems to be one of the more frequent febrile complications of recent myocardial infarction. Since the Spring of 1954, I have collected 44 cases presenting the syndrome,* 30 of which were admitted routinely to the Maimonides Hospital during the past three years. It is roughly estimated that the complication occurs in from 3% to 4% of the cases of recent myocardial infarction.

Diagnosis.—Recognition of the post-myocardial-infarction syndrome is usually not difficult if one is aware of its occurrence. It may be suspected when the febrile period following the coronary attack lasts longer than a week and is accompanied by pain of pleuropericardial type or when fever and chest pain recur. The diagnosis is confirmed when a pericardial friction rub is audible for three days or longer or when it appears late in the course of the illness. Serial x-ray studies show in such cases, more often than not, evidence of pericardial effusion, either single or combined with pleurisy and pneumonitis. In a few instances of this series, persistent sinus tachycardia during what appeared to be smooth convalescence after myocardial infarction led to the discovery of complicating pericarditis.

The diagnosis is difficult when pneumonitis is the earliest and dominant feature of the post-myocardial-infarction syndrome—also, when the symptoms of the coronary attack were mild and unrecognized and the patient presents himself first with manifestations of pleuropericarditis. It is advisable, therefore, whenever pericarditis of unknown etiology is present to include the post-myocardial-infarction syndrome in the diagnostic considerations.

The true nature of this complication has remained unrecognized until recently because its manifestations lend themselves readily to erroneous interpretation. When pericardial effusion is present "enlargement of the heart" seems to be a satisfactory radiological interpretation in the presence of myocardial infarction. Serial x-ray studies can readily correct the error in diagnosis by demonstrating shrinking of the cardiac silhouette. Recurrent chest pain and fever are often mistaken for extension of myocardial infarction. It should be remembered that when the electrocardiogram clearly indicates massive myocardial infarction prolonged or recurrent chest pain is rarely caused by extension of the infarction but more commonly by pericarditis. The differentiation is readily made by asking the crucial question of whether or not the pain is aggravated by breathing and change

* Nine more cases were observed since this paper was finished, 7 of them in the Maimonides Hospital, adding up to a total of 53.

in posture. An affirmative answer indicates that pericarditis is present; moreover, the electrocardiogram fails to show new changes which might result from extension of the myocardial lesion.

When chest pain is of pleuropericardial type or when pleural effusion is present, pulmonary infarction is an important differential diagnostic consideration. Evidence of fibrinous pericarditis or pericardial effusion, which is not usually a feature of pulmonary infarction,[10] supports the diagnosis of post-myocardial-infarction syndrome.

Recognition of the post-myocardial-infarction syndrome is important not only with regard to saving the patient and his relatives a good deal of mental anguish but also with regard to therapy. Anticoagulant therapy, which is used when extension of myocardial infarction or pulmonary infarction is diagnosed, is dangerous and contraindicated in the presence of generalized pericarditis.

Prognosis.—The outcome has been favorable in this series in all patients but the one who had been erroneously treated with anticoagulants although generalized pericarditis was diagnosed. The patient (Case 4) died of cardiac tamponade.

The complication is annoying because of pain and a tendency to relapses, but it is, on the whole, benign. When pain and cough are not a source of irritation, some patients feel strikingly well and request urgently to be allowed out of bed. To be sure, pericarditis may on occasions lead to cardiac tamponade even in the absence of anticoagulant effect, but this was not observed in the patients of this series.

Etiology.—As in the postcommissurotomy syndrome and in idiopathic pericarditis, the etiology of the syndrome complicating myocardial infarction is unknown. The severity of the infarction does not seem to be a factor, for the complication was observed both with massive infarctions and, less frequently, with mild myocardial lesions. In three instances of this series the acute infarction caused few symptoms and remained unrecognized. Yet in two of the patients a complication of marked degree developed. One sometimes wonders whether idiopathic pericarditis, especially when it affects older people, does not actually represent in some instances a post-myocardial-infarction syndrome, resulting from a small ischemic lesion of the myocardium which caused few or no symptoms and signs. The site of the myocardial infarction apparently does not exert a significant influence, for the syndrome was associated with equal numbers of anterior- and posterior-wall myocardial infarction.

It could be argued that anticoagulant therapy, by causing leakage of blood into the serous cavities, might produce symptoms and signs of pericarditis and pleuritis. Eleven patients of the group which was studied did not receive anticoagulants prior to the onset of the complication. Four of these were later treated with anticoagulants when the symptoms and signs of the syndrome were erroneously interpreted as due to extension of the myocardial infarction or to pulmonary infarction.

Attempts at culturing bacterial agents from blood and from pericardial- and pleural-aspiration fluid were unsuccessful; nor were we able to prove the presence of infection by serologic tests. Antibiotic drugs were ineffective. In this, as in many other respects, the complication of myocardial infarction resembles idiopathic pericarditis and the postcommissurotomy syndrome. A chance coincidence of idiopathic pericarditis and acute myocardial infarction is unlikely, since the incidence of the syndrome complicating myocardial infarction was about the same as that of idiopathic pericarditis alone, as observed in the Maimonides Hospital during the past three years.

Sensitization has been suggested as an etiological factor in idiopathic pericarditis and in the postcommissurotomy syndrome.[15,16] It has been shown in the experimental animal and in man that allergy might produce pericarditis, pleurisy, and

pneumonitis.[17] It may be that an antigen produced by myocardial necrosis leads, in susceptible persons, to the formation of autoantibodies which cause the post-myocardial-infarction syndrome, similar to the way in which sensitization to substances produced by surgical trauma may be the cause of the related postcommissurotomy syndrome. Studies are being conducted to gain more information on this problem.

Treatment.—Since the condition is self-limited, it may not require any treatment when discomfort is slight or absent. In every case it is of paramount importance to give the patients convincing reassurance that the complication does not represent another coronary attack and that it is perfectly benign. When pain is a disturbing factor it should be influenced by salicylates and codeine; in some instances, administration of meperidine or morphine is required.

Adrenal steroids or corticotropic hormone act almost in a specific way, relieving pain and fever within 24 hours. Prednisone was given to 14 patients, the average initial daily dosage being 35 mg. The immediate effect was invariably gratifying. The therapy was continued for six weeks in gradually diminishing dosage. Rebounds often occurred, but in the majority of cases they subsided when another short course of adrenal steroid or salicylates was given. However, in two patients, relapses repeatedly occurred whenever the daily dosage of prednisone was reduced to 15 or 10 mg., thus prolonging the course of illness to many months or even more than a year. In one of these patients withdrawal of prednisone was followed by manifestations of adrenal insufficiency. Because of such experience it is advisable to use the steroids with discretion, reserving this therapy for patients whose pain cannot be relieved by other means or whose course of illness is unduly prolonged, necessitating quick and effective therapy in order to lift their shattered morale.

Summary

The post-myocardial-infarction syndrome has been studied in 44 patients. It differs from the common "pericarditis epistenocardica" by longer duration of fever and chest pain in the initial period of illness and by relapses of fever and pleuropericardial pain; the pericardial friction rub lasts longer or occurs later than usual; there is x-ray evidence of pericardial effusion which is often associated with pleurisy and pneumonitis; recurrences are common. The exudate may be intensely hemorrhagic in the absence of anticoagulant effect.

The postmyocardial infarction syndrome is readily distinguished from those two conditions for which it has been usually mistaken: (1) from extension of myocardial infarction, by the pleuropericardial character of the pain and the absence of additional changes in the electrocardiogram, which would suggest spread of myocardial infarction, and (2) from pulmonary infarction, by the finding of evidence of pericarditis. "Enlargement of the heart," which is often erroneously diagnosed on x-ray evidence, can be ruled out by serial x-ray studies which demonstrate rapid shrinking of the heart silhouette.

It is estimated that the post-myocardial-infarction syndrome complicates from 3% to 4% of the cases of myocardial infarction. Its etiology is unknown. It is thought that sensitization by necrotic muscle tissue may be the responsible factor.

The syndrome is benign but may have a prolonged course when relapses occur repeatedly. Adrenal steroids act almost in a specific way, promptly abolishing fever and pain. Their use should be reserved for patients with severe intractable pain or prolonged course of illness.

Anticoagulant therapy is dangerous and contraindicated. A case is reported in which the use of anticoagulants in the presence of the post-myocardial-infarction syndrome led to fatal cardiac tamponade.

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Clinical Experience with the Use of Neomycin in Hepatic Coma

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The occurrence of mental changes in patients with cirrhosis following the administration of ammonium-containing substances or ammonium precursors [1,2] has stimulated the use of measures designed to reduce blood ammonia concentrations in patients with hepatic coma. Of the many regimens which have been employed, simultaneous protein withdrawal and oral administration of wide-spectrum antibiotics have been reported to give the most favorable results.[3,4] These measures have yielded a higher rate of improvement and survival in coma or impending coma than has the use of sodium glutamate, adrenal steroids, and other compounds, particularly when these are used in conjunction with continued protein feeding.[4] Although perhaps more extensively used than any other agent, glutamic acid salts have not been unanimously accepted as worth-while agents.[5-9] Promising results have been reported with the use of arginine,[10] but confirmation has been lacking.[11,12] The major criticism of the studies of both glutamate and arginine is that in the vast majority of patients therapy has been coincident with protein withdrawal. Under these circumstances, the long-term effects may be due to dietary change rather than to the agent employed.

Observations in this laboratory have indicated the efficacy of oral neomycin in reducing blood ammonia concentrations even when protein feeding was continued.[13,14] Therefore, we have studied a group of patients with neurologic changes who were treated with neomycin while oral protein administration was continued. This regimen differs from that of others in that we have deliberately administered protein to the majority of patients under study. In this series, with the exception of one patient who received arginine hydrochloride intravenously on one occasion, no other "specific" agent or measure was used. The major objective of this regimen has been the reduction of ammonia formation by reducing the intestinal bacterial flora while attempting to maintain optimal nutrition. This report is a summary of our initial clinical experience with this regimen and includes certain impressions concerning the possible limitations and hazards of this form of therapy.

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Material and Methods

Twenty-two patients with history and physical findings consistent with alcoholic cirrhosis were followed during 25 episodes of coma or impending coma. The pertinent data on each patient are shown in Table 1. This series included certain patients who received acetazolamide (Diamox) or who suffered from gastrointestinal hemorrhage. These might have been the chief factors responsible for the precipitation of hepatic coma.[15,16] Since it is likely that any extensive experience in the treatment of hepatic coma will include such patients, we are reporting our observations in these situations as well as in those patients who developed their neurological disorder spontaneously. Omitted from this study are two patients similarly treated but who died within 24 hours of the initiation of therapy and who, therefore, have been eliminated because of inadequate treatment.

The usual regimen of therapy in these patients included (1) administration of 20 to 40 gm. of protein orally or by gastric tube in divided feedings,

TABLE 1.—*Clinical and Laboratory Data*

Patient	Age	Sex	Remarks	Coma Grade		Ascites	Edema	Jaundice	Cephalin Flocc.	S. B. P. (45 Min.), %	S. Bil., Units	Alk. Phos., Units	NH_3 μg. %		Diet Protein, Gm.	Day Clin. Imp. Noted	Total Days Ther.	Result	Comment
				Initial	Max.								High	Low					
1	38	M	--	(a) I	I	+	+	+	4+	38	8.8	7.6	(a) 96	35	50	(a) 5	19	Imp. died	3 episodes of coma; deterioration under therapy
				(b) I	I								(b) 99	55		(b) 5	9		
				(c) II	II								(c) 116	35		(c) 2	11		
2	60	M	Diab. mellitus, nonalcoholic, previous abdominal-perineal resection	IV	IV	—	—	—	4+	49	4.6	3.3	327	67	80	2	5	Imp. died	Partial mental clearing, severe hyponatremia
3	46	M	Hematemesis prior to & during therapy	III	III	—	—	—	4+	12	1.8	1.7	168	31	70	6	15	Imp. died	Repeated bleeding, died after ligation of varices
4	55	M	Intermittent stupor for 6 wk., acetazolamide therapy	II	III	+	+	+	2+	—	2.0	2.9	166	22	10	3	20	Imp. died	Severe hyponatremia
5	45	M	--	II	III	+	+	+	4+	—	5.6	9.6	94	30	90	3	4	Imp. died	Died suddenly while doing well; no autopsy
6	63	M	Portocaval shunt 1 yr. prior to episode	I	I	—	—	—	4+	80	—	9.2	138	36	50	6	11	Imp. lived	—
7	43	M	Hematemesis from gastric ulcer	I	I	—	—	+	4+	25	6.9	4.5	116	61	0	3	4	Imp. lived	—
8	32	M	Bleeding varices prior to & during therapy	I	II	+	+	0	3+	23	2.2	—	95	10	0	1	4	Imp., lived	Lived 9 mo; died after subsequent hemorrhage & ligation of varices
9	54	M	—	II	III	+	+	+	2+	—	5.5	2.9	187	30	20	6	11	Imp., died	Progressive icterus & anorexia
10	64	M	2d episode treated 2 mo. after 1st	(a) II	III	—	+	±	4+	32	1.0	2.3	88	20	50	2	4	Imp., living	(a) 12 gm/day
				(b) I	I								120	32	50	5	6		(b) 8 gm/day (neomycin)
11	59	M	Chronic pulmonary emphysema, repeated previous episodes of jaundice	II	II	—	+	—	1+	2	0.9	2.3	96	25	40	1	13	Imp., living	
12	48	M	Acetazolamide administration, gout, hypertension	IV	IV	—	—	—	1+	25	1.0	—	229	23	0 for 48 hr., then 35	2	9	Imp., living	

13	48	M	Previous episode of impending coma	I	I	+	+	+	4+	—	9.4	4.5	130	80	50	3	7	Imp., living	
14	50	M	Previous renal tuberculosis	III	III	+	0	+	4+	—	4.6	6:9	111	13	25	3	6	Imp., living	
15	49	F	—	I	III	0	0	+	4+	40	8.4	6.9	75 initial	106 terminal	30	—	14	No imp., died	8 gm. doses 9 days, then 12 gm. daily
16	60	M	Gastrectomy for ulcer 2 yr. previously	IV	IV	+	+	0	4+	2.8	—	3.1	109 initial	121 terminal	85 for 1 day, then 0	—	4	No imp., died	Received 25 gm. arginine I. V. on 3d day of neomycin
17	88	M	Bleeding from varices	I	II	+	+	+	3+	76	7.8	3.1	79	61	50	6	6	Imp., died	Transiently rational on day of death
18	64	M	Bleeding from varices	I	I	+	0	0	4+	—	1.4	1.8	Not done		40	3	5	Imp., living until surgery	Remained clear until after surgery; had 5 gm. neomycin in 24 hr. prior to surgery; intermittent therapy begun 3 days after surgery; pancreatitis at autopsy
19	50	M	—	I	I	0	0	+	—	38	23.8	5.2	133	29	40	5	14	Imp., living	
20	34	F	Transferred from another hospital 4 days after therapy was begun	IV	IV	0	0	+	—	—	16.4	12.7	?	63 *	20	2	5	Imp., died	* After 4 days of neomycin in 4 to 6 gm. doses. Died suddenly after being rational for 48 hr.
21	55	M	Acetazolamide administration; bleeding varices during therapy	II	II	+	+	+	3+	—	16.0	3.1	Not done		25	3	8	Imp., died	Developed hyponatremia & azotemia
22	45	F	Bleeding varices	III	III	+	+	+	4+	36	3.2	—	Not done		0	3	11	Imp., living	Portacaval shunt without difficulty under neomycin therapy

* This was determind after neomycin had been given.

except four patients who received no protein for 48 hours; (2) oral neomycin,* 12 gm. daily, given on a schedule of 3 gm. every six hours orally or by tube; (3) intravenous dextrose, usually containing vitamins and potassium chloride; (4) in patients with bleeding esophageal varices insertion of a Sengstaken tube and control of bleeding attempted by the use of balloon compression (Such blood as was in the stomach was usually removed by aspiration. These patients were given transfusions as needed), and (5) parenteral administration of penicillin and streptomycin to the majority of patients in an attempt to prevent complications such as pneumonia. Omitted from routine use were enemas, cathartics, or other measures for emptying the intestinal tract, with the exception of the cathartic effect of the neomycin.

The neurological state in these patients has been personally assessed by one or both of us, and the following gradation of stages of coma from I to IV has been used: Grade I, overt confusion, usually associated with flapping tremor; Grade II, light stupor, in which the patient was drowsy or lethargic but easily aroused; Grade III, deep stupor, in which the patient was responsive only to painful stimuli, and Grade IV, coma, in which the patient was unresponsive to painful stimuli. It is apparent that for purposes of comparison our Grades I and II might be called impending coma and Grades III and IV classified as coma. Throughout this discussion, however, the term coma has been used to denote the presence of any typical neurologic changes attributable to ammonia intoxication. Recovery is used to describe those patients who regained a stable alert state or who were able to be discharged from the hospital. Improvement denotes a decrease in the degree of the neurological change or a regaining of consciousness, regardless of eventual outcome.

Ammonia determinations have been carried out on peripheral venous blood by a modification of the method of Conway.[17,18] Although the use of antecubital venous blood may be subject to error owing to the presence of palmar erythema in certain patients,[19] the relative changes from day to day are probably valid on the assumption that the degree of arteriovenous shunting in the palms did not change significantly during the course of the acute episode and the recovery therefrom. The determinations were performed in a nonfasting state in order that, insofar as possible, maximal blood ammonia could be determined in these patients.

In most patients, particularly those with fluid retention, repeated sodium and potassium determinations were performed at intervals. These showed no obvious relation to the neurological state, although the appearance of marked hyponatremia appeared to affect deleteriously the eventual outcome. Our experience has been similar, therefore, to that of Hecker and Sherlock.[20]

* Supplied as Mycifradin Sulfate by the Upjohn Company, Kalamazoo, Mich. Dose used refers to grams of neomycin sulfate and represents 8.4 gm. of neomycin base.

Results

Of the 22 patients studied, 11 died, but prior to death 9 of these showed improvement. Of the 25 episodes of coma, recovery was noted in 14 instances, one patient having experienced 3 episodes and another patient, 2 episodes. Twenty-three instances of improvement were recorded in the twenty-five episodes (Table 2).

TABLE 2.—*Neomycin Therapy in Hepatic "Coma"*

	Total	Lived	Died	Improved
Patients	22	11	11	20
Episodes of coma	25	14	11	23
Received dietary protein	18	7	11	16
Received protein either dietary or in blood	21	10	11	19
Blood NH_3 done	18	8	10	16
NH_3 decrease with therapy	16	8	8	16

Eighteen patients received protein from the beginning of therapy with neomycin, and, of these, seven lived and eleven died, but improvement was noted prior to death in nine of the latter. Four patients received no dietary protein, and all survived, but of these, three had bleeding and thus had protein within the intestinal tract in excess of that present in the fasting state.

A decrease in blood ammonia during therapy was observed in 16 of the 18 patients in whom it was determined. Of those whose ammonia levels fell, eight lived and eight died, with all patients showing some improvement prior to the final outcome. Death occurred in both patients in whom the ammonia did not fall during neomycin therapy, and neither patient exhibited improvement.

Survival was far commoner in patients in whom therapy was initiated when coma was only Grade I, but little distinction between Grades II, III, and IV could be drawn

TABLE 3.—*Relationship of Therapeutic Result to Neurologic Change*

	Coma Grade	Patients	Lived	Died	Improved
At beginning of therapy	I	9	7	2	8
	II	6	1	5	6
	III	3	2	1	3
	IV	4	1	3	3
Maximal neurologic change	I	4	4	0	4
	II	6	3	3	6
	III	8	3	5	7
	IV	4	1	3	3

from the results obtained (Table 3). Six patients showed further progression of the neurological disease by one or more grades beyond the original state (Table 3). Reclassification on this basis revealed that survival was less likely with greater maximal neurological aberration. Seven of ten patients in Grades I and II survived, while only four of thirteen patients who developed Grade III or IV coma survived. Of the six whose neurological state became worse, only two lived, although three others showed improvement before death.

In an attempt to assess the results in terms of amount of protein given during the first two days, the patients have been divided into one group who received 25 gm. of protein or less and another group who received more than 25 gm. of protein from the beginning of treatment (Table 4). Of the 13 patients receiving more than 25 gm. of protein, 6 survived and 11 showed improvement, while of the 9 patients receiving 25 gm. or less, 5 survived and 9 showed improvement. Since patients with bleeding from varices or ulcer are subjected to protein within the intestine in excess of that which is fed and also suffer other physiologic derangement from anemia and shock, the results have also been analyzed with regard to whether or not hemorrhage occurred. The results in patients who were not hemorrhaging are accordingly based upon very small numbers. Of the 10 who received more than 25 gm. of protein, 5 survived and 8 showed improvement, while in the group receiving less than 25 gm., 2 survived and 6 showed improvement. It should be pointed out that these patients were not treated under a planned program of alternation of cases, and an element of bias may have been present to the extent that the more severely ill patients were given smaller amounts of protein or none.

TABLE 4.—*Relationship of Protein Feeding During First Two Days to Result*

Dietary Protein	Patients	Lived	Died	Improved
Nonbleeders				
Less than 25 gm.	5	2	3	5
More than 25 gm.	10	5	5	8
Bleeders				
Less than 25 gm.	4	3	1	4
More than 25 gm.	3	1	2	3
Total				
Less than 25 gm.	9	5	4	9
More than 25 gm.	13	6	7	11

Of the various findings on physical examination none showed correlations with the final result, except for jaundice, ascites, or edema. Patients with these findings appeared to have lower survival rates than the patients without these findings (Table 5).

TABLE 5.—*Relationship of Clinical Finding to Therapeutic Result*

	Total	Survived	Died
Bleeding	7 *	4 *	3
Jaundice	13	5	8
Ascites	11	4	7
Edema	12	5	7
Hepatomegaly	18	9	9
Splenomegaly	7	4	3
Abdominal collateral veins	11	6	5
Spider angiomata	14	6	8
Palmar erythema	7	4	3
Previous portacaval shunt	1	1	0

* One patient bled from duodenal ulcer.

Analysis of the relationship of various laboratory determinations to the therapeutic result indicates that not only the presence of hyperbilirubinemia but also the degree of bilirubin elevation may alter the prognosis. Of 12 patients with a level greater than 3 mg. per 100 ml., 4 survived, and of the 9 patients with a bilirubin greater than 5 mg. per 100 ml., only 2 survived (Table 6).

TABLE 6.—*Relationship of Laboratory Finding to Therapeutic Result*

Test	Patients in Whom Determined, No.	Total with Abnormal Results	Survived	Died
Ceph. flocculation	20	16	7	9
Sulfobromophthalein	14	13	7	6
Prothrombin < 50%	22	19	8	11
Bilirubin total > 1.0	20	17	6	11
Bilirubin total > 3.0		12	4	8
Bilirubin total > 5.0		9	2	7
Alkaline phos. > 5.0	18	7	2	5
Serum alb. < 3 gm. %	21	8	4	4

The presence of visible abdominal collateral veins, which might be related to the degree of spontaneous shunting of blood around the liver, did not have any remarkable value in prognosis.

Seven of the patients had bleeding episodes, one from a duodenal ulcer. Four of these, including the patient with the bleeding ulcer, survived. Four of the patients had surgical procedures in attempts to control bleeding, and two of these survived. Of the two patients in whom acetazolamide may have played a contributory part in the development of their neurological symptoms, one patient died and the other survived. One patient who had had a previous portacaval shunt survived the episode of coma.

In patients who demonstrated a fall in blood ammonia, such was usually apparent in 72 hours or less, and the ammonia concentration remained low unless therapy was interrupted. In some patients a marked decrease was noted as early as 24 hours after initiation of therapy. Whether this early fall was due to reduction in the amount of protein ingested or was the result of a decrease in the intestinal flora cannot be determined. The duration of neomycin therapy varied from 4 to 20 days. In one patient who was followed through three episodes of impending coma, the administration of neomycin with a 50 gm. protein diet was followed by clinical improvement and significant lowering of the blood ammonia concentration in each instance (Fig. 1). After the third episode, however, despite continuous therapy, his condition deteriorated and, although he was responsive until the last few hours, death occurred on the 53d hospital day.

A typical example of an excellent response was Patient 14, who was admitted with Grade III coma and who had received neomycin for approximately 24 hours before entry. Continuation of neomycin and administration of a 25 gm. protein diet by tube feeding yielded improvement, which was clinically apparent by the third day. The blood ammonia concentration had fallen significantly 24 hours earlier (Fig. 2). It was not uncommon to observe a fall in blood ammonia prior to the clinical or neurological improvement in this series of patients.

The course of a patient who developed coma after a bleeding episode is demon-

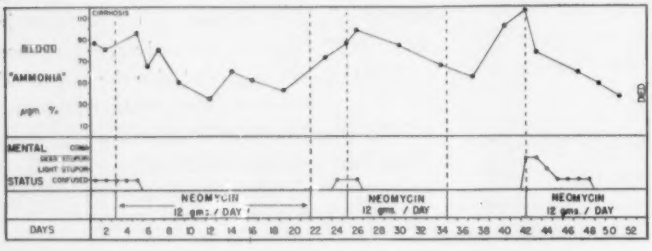

Fig. 1 (Patient 1).—Repeated episodes of neurologic change with response to neomycin; 50 gm. protein diet throughout.

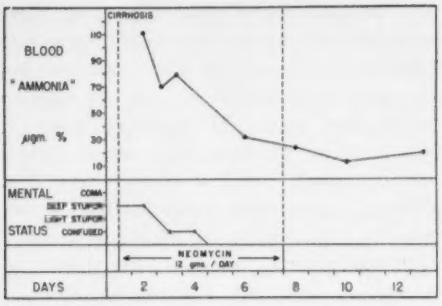

Fig. 2 (Patient 14).—Recovery from deep stupor; 25 gm. diet by tube and then orally.

strated by Patient 22. This was a 45-year-old woman who had had known cirrhosis for approximately two years and who entered with bleeding from esophageal varices. After blood transfusions and the attainment of hemostasis with the use of a Sengstaken tube, her condition appeared to be stable 48 hours after admission. She then developed neurological changes and rapidly progressed to deep stupor. Neomycin therapy was begun on the third hospital day. Grade IV coma occurred on the fourth day, but progressive improvement followed thereafter, and by the sixth hospital day (the third day of neomycin) she was alert and responsive. The dose of neomycin was reduced to 8 gm. on the 6th day of therapy, and this was continued until after a portacaval shunt was performed without difficulty 12 days after the initiation of neomycin.

An instance in which neomycin therapy was associated with improvement and continued therapy may have prevented the onset of coma was seen in Patient 8 (Fig. 3). This patient entered for treatment of ascites and subsequently bled from esophageal varices. Within 12 hours of the onset of bleeding he became confused, and neomycin was begun. This was given through the Sengstaken tube which controlled the bleeding while it was inflated. The confusion cleared in 24 hours. Repeated bleeding occurred on three occasions at approximately 48-hour intervals when attempts to remove the tube were made, but confusion did not recur. Cessation of neomycin therapy on the third day for 36 hours was associated with a rise in blood ammonia, which fell again as treatment was reinstituted. The ammonia remained within the normal range throughout the repeated hemorrhages which occurred. On the 12th hospital day the tube was withdrawn without subsequent bleeding, and neomycin therapy was stopped after the 15th day.

Analysis of the patients who failed to survive reveals only two (Patient 16 and Patient 15) in whom neomycin appeared to have no effect. In these patients no ammonia change was noted, and their clinical state became progressively worse. Aside from the possibilities that no hepatic removal of ammonia occurred or that the bacterial flora was not sufficiently altered to reduce ammonia formation, no explanation for the failure of therapy in these patients is available. In two other patients (Patient 9 and Patient 1), death appeared to be due to progressive deterioration in liver function but decreases in blood ammonia were observed.

In Patient 5 and Patient 20, sudden death occurred after marked improvement had

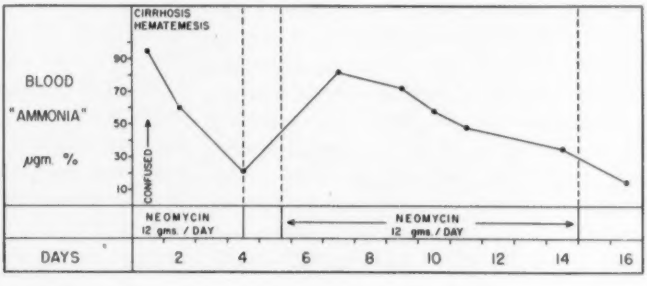

Fig. 3 (Patient 8).—Recovery from confusion and prevention of recurrence of neurologic change during bleeding from varices. Bleeding recurred on Days 3, 6, and 8 when Sengstaken tube was removed temporarily.

occurred and while they appeared to be alert and rational. Unfortunately, no autopsy was obtained in these patients, and the cause of death could not be determined. It is of note that Patient 20 had a serum sodium of 116 mEq. per liter just prior to death. No indication that these deaths might have been due to the effects of neomycin therapy was present, but this possibility cannot yet be excluded.

Uncontrolled bleeding was probably chiefly responsible for death in Patients 17 and 3. This occurred despite use of balloon tamponade in both patients and transthoracic ligation of varices in Patient 3). Marked hyponatremia may have been a contributory factor in three other patients. Two of these had ascites and edema (Patient 21 and Patient 4), and the third developed coma and hyponatremia after resection of a carcinoma of the rectum and prolonged intestinal aspiration.

In this series of patients, no serious toxic effects were observed which could be directly attributed to the use of neomycin. In nearly all patients the occurrence of three to seven loose stools per day was observed. This was seldom disturbing to the patient and was not associated with significant abdominal cramping. The occurrence of this diarrhea, however, prompted careful attention to potassium loss. These patients usually received vitamin K parenterally, and no prothrombin depletion attributable to neomycin therapy was observed.

Comment

The results obtained in this series of patients are comparable to the results obtained by others who used protein withdrawal and chlortetracycline.[3,4] Of the 66 patients observed by Sherlock, Summerskill, and Dawson,[3] only 30 can be considered comparable to the cases reported herein. Analysis of that series indicates that 14 of the patients recovered. The patients reviewed by Summerskill, Wolfe, and Davidson[4] were divided into two groups, one in which protein withdrawal and antibiotic administration were the chief measures and another in which protein was continued, with various other measures being used in addition. Of the 34 patients in the first group, 13 recovered, while in the group in whom protein administration was continued only 2 of 30 recovered. The efficacy of neomycin as administered to our patients may perhaps be judged by the fact that our patients had a recovery rate of 11 out of 22 despite the administration of protein. In evaluating survival in coma, it has been pointed out[3] that prior to the present awareness of the early mental and neurological changes in impending coma therapy was judged by results obtained in patients who lost consciousness. On the basis of this criterion alone, it becomes apparent that only 4 of 12 unconscious patients in our series survived and 6 other patients showed improvement prior to death. This recovery rate is not unlike that observed with wide-spectrum antibiotics and protein withdrawal. It is of note, however, that Summerskill, Wolfe, and Davidson,[4] in contrast to our experience, found somewhat higher recovery rates in patients who were in coma at the time of initiation of therapy than in patients who were not in coma. The poor prognosis associated with elevated serum bilirubin or the presence of ascites has also been observed in previous studies.[3,4]

The possibility of bias in the selection of which patients were to receive protein was mentioned above, but the role of protein when neomycin is used may bear further consideration. Although it may be pointed out that approximately one-half of our patients received extremely small amounts of protein or none during the initial stages of therapy, it is of note that after 48 to 72 hours of therapy these patients were able to tolerate protein in larger amounts, without recurrence of coma when neomycin was continued. This occurred even in some patients who were severely ill and in whom it was judged desirable to attempt to improve their nutrition by ad-

ministration of protein orally. In a few patients the complete withdrawal of protein after the first few days did not appear to alter the prognosis, but it must be noted that these were the most severely ill and probably no therapeutic measures would have been effective. Our experience to this time would indicate that with adequate reduction in bacterial flora of the intestine protein may be administered safely, but whether or not administration of protein is more effective than provision of adequate calories alone cannot be determined.

The efficacy of neomycin as well as other agents will be determined by the type of patient and the severity of the illness. The probable effect of neomycin is that of reducing the intestinal bacterial flora, and blood ammonia concentration cannot be expected to fall unless the liver and other tissues are capable of removing the ammonia already present. Thus, in a patient with severe and rapidly progressing disease, where these mechanisms are badly damaged, it is likely that neomycin will be less effective.

In view of the often noted discrepancy between the blood ammonia concentration and the neurological state of the patient, other factors in addition to or separate from ammonia may be operative in producing neurological changes. The role of other compounds, such as phenols [21] or amines,[22] remains to be evaluated. It is possible, however, in view of the marked alteration in intestinal flora produced by neomycin, that this agent may reduce the formation of other toxic compounds. It is of note that the stools of patients receiving neomycin are nearly odorless, suggesting that marked reduction in some compounds ordinarily found in the feces has occurred. If such reduction reflects suppression of formation of toxic compounds, the effect of production of a bacteria-poor intestine may be beneficial by means other than that of reduced ammonia formation.

In view of the probability that the liver is constantly perfused by toxic products of intestinal bacterial metabolism, the use of agents to alter bacterial flora in cirrhotic patients, even in the absence of neurologic disease, may be rationally considered. Martini, Phear, Ruebner, and Sherlock [23] have reported increased numbers of bacteria in cirrhotic patients and the presence of bacteria in the jejunum and duodenum of such persons, in contrast to normals. Chronic administration of neomycin to all cirrhotic patients, even in the absence of neurologic aberration, should nevertheless await further studies of its metabolic effects, in view of the demonstrated catabolic effects of other antibiotics.[24,25]

The efficacy of neomycin in patients with bleeding varices is at best difficult to evaluate. However, in view of the frequent occurrence of neurologic changes in these patients, prevention of coma and lowering of blood ammonia would appear to indicate a beneficial effect of neomycin. This is particularly true in view of the observation that not only does blood in the intestinal tract elevate blood ammonia [26] but also infusion of banked blood may be a source of ammonia.[27]

The therapeutic regimen employed in this series of patients is obviously not ideal, but it has allowed us to evaluate a specific agent when used in association with continued protein administration. In view of the experience obtained by others, complete protein withdrawal for 48 hours after neomycin is initiated would appear desirable in order to allow maximal reduction in ammonia formation prior to the reduction in bacterial flora. In addition, there is good rationale and some evidence for the beneficial effects of the administration of cathartics and enemas.[4] Once bowel sterilization has been obtained, however, it would appear desirable to administer some protein by mouth in order to hasten the repletion of protein and other nutrients in the patient with severe liver disease. The dose of neomycin required for such a therapeutic regimen has not yet been established, although we have observed failure of ade-

quate control of blood ammonia levels in a patient receiving 4 gm. of neomycin daily.[13] In a few patients previously studied, doses of 8 gm. daily appeared to yield satisfactory changes in blood ammonia.[14] The present dose of 12 gm. may be excessive, and further studies will be necessary to establish the minimal effective dose.

Summary

Clinical experience with the use of neomycin in the management of hepatic coma has been reviewed. In a series of 22 patients receiving neomycin, 11 survived and 9 others improved prior to death. Dietary protein in varying amounts was administered from the beginning of neomycin therapy to 18 patients. Three others who were bleeding were presumed to have protein in the intestinal tract at the time of initiation of therapy. No significant difference in survival rate was observed between patients receiving more than 25 gm. of protein and those receiving less than 25 gm. An unfavorable prognosis in these patients was found to be associated with increasing depth of coma after therapy was initiated and with the presence of jaundice.

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Addendum

During the preparation of this paper, two other reports on the use of neomycin in hepatic coma have appeared.[28,29] These indicate results similar to those obtained in this study.

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Some Less Familiar Roentgen Manifestations of Intrathoracic Histoplasmosis

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After the demonstration of a high degree of correlation between histoplasmin skin sensitivity and intrathoracic calcification in the Ohio and Mississippi River basins it was predicted that cases of active histoplasmosis would be recognized with considerably increased frequency. This prediction appears to have materialized. The active form of the disease is now commonly encountered, and numerous verified cases have been recorded in the recent literature.[1-8]

Various roentgen manifestations of intrathoracic histoplasmosis have been depicted and their course described.[9-14] For the most part, these findings have fallen into three main categories: (1) an acute disseminated form with miliary or small patchy densities diffusely distributed throughout the lungs, sometimes encountered in epidemics[8,15,16]; (2) a localized pneumonic form, and (3) the solitary nodule ("coin" lesion, histoplasmoma) of chronic and asymptomatic nature. Each of these types may be associated with hilar and/or mediastinal lymph node enlargement of variable degree and extent, the so-called primary complex. In some cases the lymph node enlargement may be the sole roentgen manifestation of the disease.

The healing phase is commonly accompanied by the deposition of calcium in the pulmonary lesions and lymph nodes, though complete clearing of the lungs without calcification is not unusual. The persistent spherical focus, or histoplasmoma, may represent either the end-result of an earlier pneumonic infiltrate or a filled-in cavity and is generally considered inactive. It often contains a solid or laminated central core of calcification, best demonstrated by tomography.[17]

These well-known roentgen manifestations of intrathoracic histoplasmosis are by no means the only ones encountered in the disease. Other patterns do occur, some with fair frequency, and here, too, the diagnosis may at times be suspected from the roentgen appearance and course. A discussion of some of these less familiar patterns follows.

Fibrocavitary Histoplasmosis

Fibrocavitary histoplasmosis has generally been considered a rare form of the disease. Furcolow and Brasher[3] could find only 16 cases reported up to 1956. However, in a survey of 600 unselected patients in a tuberculosis hospital in Missouri they were able to demonstrate Histoplasma capsulatum in the sputum in 14 cases (2.3%) and positive serologic tests for histoplasmosis in an additional 29. Thus, a number of patients in this sanatorium had histoplasmosis rather than tuberculosis, and this was mostly of the chronic progressive fibrocavitary type.

This form of histoplasmosis is seen chiefly among elderly men who are chronically ill with symptoms and signs closely simulating those of active chronic fibroid tuberculosis.[18] Roentgenographically, this similarity is maintained. Usually there is fibrotic involvement of one or both upper

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lobes, with hilar elevation, retraction of the pulmonary septa, and displacement of the mediastinal structures. Cavitation is a prominent feature and is obvious in most, if not all, cases. The process may remain stationary or even rarely regress, but more often there is slow progression over a period of months or years, with involvement of more and more lung parenchyma and ultimately death. The sputum usually abounds with H. capsulatum, and the skin and complement-fixation tests are often positive. Occasionally tuberculosis and histoplasmosis may coexist,[18,19] and the sputum may be positive for both organisms.*

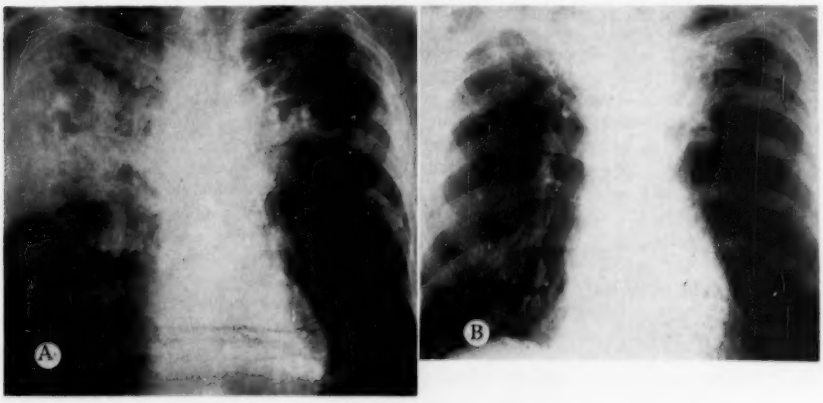
Our experience with this form of histoplasmosis is based on five cases, three of which have been included in the paper of Bronson and Schwarz.[13] In general, the clinical and roentgen findings resembled those described above. The youngest patient was 38 years of age, and the oldest, 76. All were white men. Each had been hospitalized in a tuberculosis sanatorium, where the correct diagnosis was first established. A positive histoplasmin skin test was found in four cases, and a positive tuberculin, in three. The complement-fixation test for histoplasmosis was positive in three and negative in two. In the positive cases the highest titers obtained were 1:2048, 1:256, and 1:512, respectively. Sputum cultures were repeatedly positive for H. capsulatum in four cases, and negative, in one. In the latter, H. capsulatum was grown on culture of a triturate obtained from a surgically resected segment of lung. Multiple smears and cultures for tubercle bacilli were negative in each case.

The admission chest roentgenograms revealed widespread disease, bilateral in three and unilateral in two. In each case at least one upper lobe was extensively affected. That the process was essentially fibrotic in nature was evident from the duration of the disease; the irregular, dense, and sometimes linear appearance of the infiltrate, and the contraction of the thorax with retraction of the hilar and mediastinal structures. Extensive cavitation was present in all cases. The cavities were generally large and multiple, sometimes containing fluid levels. One patient terminally developed a spontaneous pneumothorax.

In three cases the lesions progressed; in one they remained stationary, while in one marked regression occurred (Case 1). The rate of change varied from case to case.

* A few cases of histoplasmosis associated with lymphoma have also been reported.[4,20]

Fig. 1 (Case 1).—Fibrocavitary histoplasmosis. *A*, October, 1955. Pulmonary infiltrate with multiple small cavities in the upper half of the right lung and fine nodular densities in the lower half. A large multiloculated cavity is seen in the left upper lobe. *B*. August, 1956. There has been marked contraction of the upper lobe lesions, with shrinkage of the cavities and complete clearing of the lower right lung.



In one patient there was rapid extension over an eight-month period, with death. In another, the lesions remained unchanged roentgenographically for several years and then enlarged, the patient ultimately dying of the disease. In a third case gradual extension occurred over a one-year period, after which resection was performed. A small cavitary lesion has since appeared in the opposite lung. Another patient showed an unchanging roentgen picture for two years and has remained alive with active disease. The remaining case showed striking improvement and is herewith reported.

CASE 1 (Reported by courtesy of Dr. Herman Nimitz).—A 65-year-old white man was admitted to Dunham Tuberculosis Hospital, Cincinnati, in October, 1955, acutely ill with high fever and severe productive cough. He had lost much weight and was in a cachectic state. A roentgen diagnosis of extensive tuberculosis had been made at another hospital.

Admission chest roentgenogram (Fig. 1*A*) revealed extensive infiltrate in the upper half of the right lung, honeycombed with cavities. The lower half of the right lung showed numerous fine mottled densities. A large multiloculated cavity surrounded by a small amount of infiltrate was evident in the left upper lobe. The lower half of the left lung appeared clear. The trachea was deviated toward the left.

Many smears and cultures of the sputum failed to reveal tubercle bacilli. Tuberculin skin tests were negative, but a histoplasmin skin test (1:100) was positive. A complement-fixation test for histoplasmosis was also positive, at first in dilution of 1:128 and later, 1:256. H. capsulatum was grown repeatedly on cultures of the sputum.

Clinically and roentgenographically the patient showed marked improvement over the next eight months, during which time he was treated with streptomycin, isoniazid, penicillin, and sulfisoxazole (Gantrisin). Sputum cultures became negative, and his chest film at the time of discharge, in August, 1956, (Fig. 1*B*) showed contraction of the lesions in both upper lobes and marked clearing elsewhere in the lungs. The cavities had shrunk considerably. Both hila were greatly elevated, and the trachea now appeared to be deviated toward the right. The patient failed to keep his follow-up appointment.

Comment.—The clinical and roentgen appearance of fibrocavitary histoplasmosis may be closely simulated by tuberculosis, by other fungus infections, and by certain diseases of bacterial origin, such as chronic Friedländer's pneumonia. Ordinarily, the extensive cavitation associated with pneumonitis of these varieties is accompanied by expectoration of large numbers of the causative organisms, so that appropriate sputum examinations usually disclose the diagnosis. Since this applies most often to chronic fibroid tuberculosis, it follows that any patient presenting a fibrocavitary roentgen pattern and in whose sputum tubercle bacilli cannot be demonstrated should be studied for histoplasmosis. If the sputum is negative for H. capsulatum, skin and serologic tests for histoplasmosis should be performed. If this procedure is followed in tuberculosis sanatoria located in the area of endemism of histoplasmosis, the yield should be especially high. In the endemic area, even patients with known tuberculosis should probably be examined for histoplasmosis, since coexistence of the two diseases is not uncommon.

Enlarging Histoplasmoma

Pulmonary histoplasmoma are generally regarded as inactive lesions, since they cause no symptoms and appear to remain roentgenologically stationary for prolonged intervals. Although yeast forms consistent with H. capsulatum have often been demonstrated in their centers by the use of the Gridley [21] or Grocott [22] stains, cultures of triturates of the nodules are almost invariably sterile. Peabody [14] obtained a positive culture in only 1 of 30 cases. That the histoplasmoma may enlarge radiographically is illustrated by the following case.

CASE 2 (Reported by courtesy of Dr. Henry Felson).—A 46-year-old white man had a chest roentgenogram made in October, 1954, as part of a routine physical examination. He was completely asymptomatic, and his past history and physical examination were noncontributory. A nodule 1.4 cm. in diameter was discovered in the left third anterior interspace. It contained a definite central calcification (Fig. 2*A*). Histoplasmin and tuberculin skin tests were positive, while coccidioidin and blastomycin skin tests were negative.

The patient remained asymptomatic, and repeated chest roentgenograms showed no change until

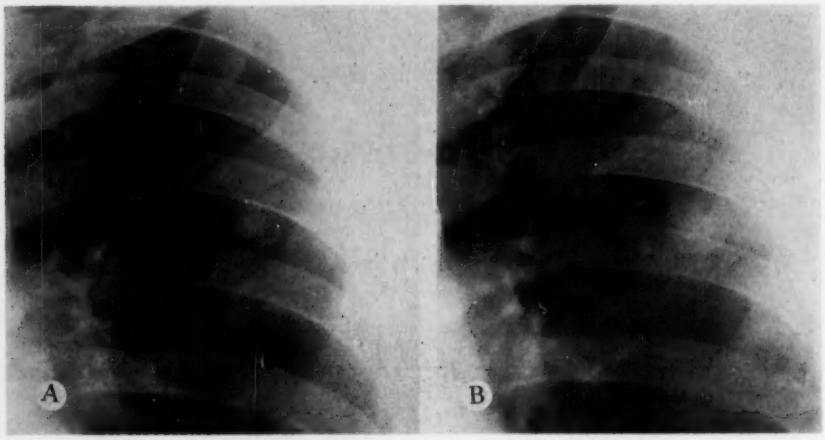


Fig. 2 (Case 2).—Enlarging histoplasmoma. *A*, October, 1954. Nodule in left third interspace measuring 1.4 cm. in diameter and containing a laminated calcification. *B*, February, 1957. Similar technical and magnification factors as in *A*. The nodule now measures 2 cm. in diameter. (Reproduced with permission from *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.*[30])

February, 1957, when the nodule was found to have enlarged to a diameter of 2 cm. (Fig. 2*B*). Tomography confirmed the presence of the central calcification.

A segmental resection was done by Dr. Richard Overholt in April, 1957. The lesion was found to be well circumscribed, with a caseocalcareous center. Microscopically it proved to be a granulomatous inflammatory nodule. Although organisms were not grown on culture, Gridley and Grocott stains revealed numerous yeast forms typical of H. capsulatum.

Comment.—We have recently encountered a second case of slowly enlarging histoplasma, and Peabody[14] has reported two similar cases. It should be emphasized, however, that these cases are exceptional and that the vast majority of histoplasmomas remain unchanged over prolonged periods of observation. Nor have we ever seen them give rise to new nodules or pulmonary infiltrates. Furthermore, they are almost invariably culturally sterile and histologically quiescent. Taking all these facts into consideration, one must conclude that these lesions represent a spent form of histoplasmosis.

Broncholithiasis

The overwhelming majority of broncholiths are attributable to erosion of calcific foci from the lung parenchyma or tracheobronchial lymph nodes into a bronchus. It has been generally assumed that quiescent tuberculosis is the underlying cause of these calcific foci.[23] However, in the endemic area, one must consider the possibility that histoplasmosis, rather than tuberculosis, provides the background for broncholiths.

Broncholithiasis is not rare in the Cincinnati area. We have seen at least 12 cases in the past five years, and it is probable that others have gone unrecognized. The following case is believed to be the first reported example in which H. capsulatum has been demonstrated in a broncholith.

Case 3 (Previously published by Baum, Bernstein, and Schwarz[24]).—A 53-year-old white man was admitted to Jewish Hospital, in Cincinnati, on Aug. 26, 1956, because of a severe hemoptysis. He had a slight fever and right upper chest pain. Rales were heard over the right lung posteriorly.

Chest roentgenograms revealed a wedge-shaped area of infiltration in the apical segment of the right upper lobe, with its apex extending toward the hilum. Tomograms of the right lung (Fig. 3*A*) revealed two fragments of calcium measuring 6 mm. and 8 mm. in largest diameter, respectively, lying in close proximity to the origin of the apical-segment bronchus of the right upper lobe. Bronchography findings appeared normal, but the apical-segment bronchus was not clearly delineated, and contrast material was not present in this segment.

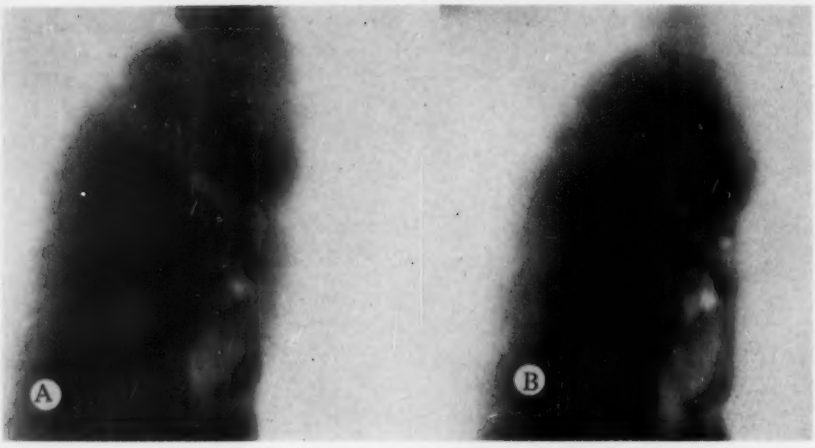


Fig. 3 (Case 3.)—Histoplasmic broncholith. *A*, Sept. 20, 1956. Tomogram of right upper lobe. Wedge-shaped infiltrate extending upward from the right hilum; two fragments of calcium are seen at the proximal border of the infiltrate. *B*, Oct. 10, 1956. Tomogram made at the same level. The lateral fragment is no longer present. The infiltrate has almost completely cleared. (Reproduced with permission from *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.*[50])

On Oct. 2, the patient coughed up an irregular fragment of calcium. Subsequent tomograms showed that the larger more peripheral calcific fragment had disappeared (Fig. 3*B*). The segmental pneumonia gradually subsided. The expectorated calculus measured 6×5×5 mm. and consisted of incompletely calcified necrotic material. Gridley stains of tissue sections of the decalcified specimen revealed numerous yeast cells morphologically indentical with H. capsulatum. Cultures were negative.

Comment.—Baum, Bernstein, and Schwarz [24] included a second case of broncholithiasis in their report. The demonstration of H. capsulatum in the only two instances in which a broncholith was studied for this organism and the frequency with which Straub and Schwarz [25] demonstrated the organism in pulmonary and mediastinal calcifications at autopsy lend support to the belief that histoplasmosis, rather than tuberculosis, is the underlying cause of most cases of broncholithiasis in this area.

Traction Diverticulum of the Esophagus

Another sequel of long-standing inflammation of lymph nodes is the traction diverticulum of the esophagus. The contraction of the fibrous tissue in and around the mediastinal nodes, particularly those in the carinal region, draws out the adjacent esophageal wall, resulting in a diverticulum. Here, too, the underlying cause of the lymph node disease has been widely attributed to tuberculosis. It is probable that in our area, at least, histoplasmosis may be responsible for many esophageal traction diverticula. Peabody [26] cited a case of esophageal diverticulum, complicated by tracheobronchial fistula and expectoration of a broncholith, in which H. capsulatum was demonstrated.

The following case suggests this etiology. It is the only example in the present series in which confirmation is lacking, but the demonstration is so vivid that I could not resist the temptation to include it in this report.

Case 4.—A Negro man, a 26-year-old physician, came to Cincinnati from New York City in July, 1953, never having been west of the Alleghenies prior to that time. In November, 1953, he developed mild dysphagia, intermittent at first but subsequently more persistent. Except for heartburn, no other symptoms were elicited. There had been no cough, night sweats, fever, or weight loss. Past history was noncontributory, except that a positive tuberculin skin test had been demonstrated on several occasions since the age of 19. Physical

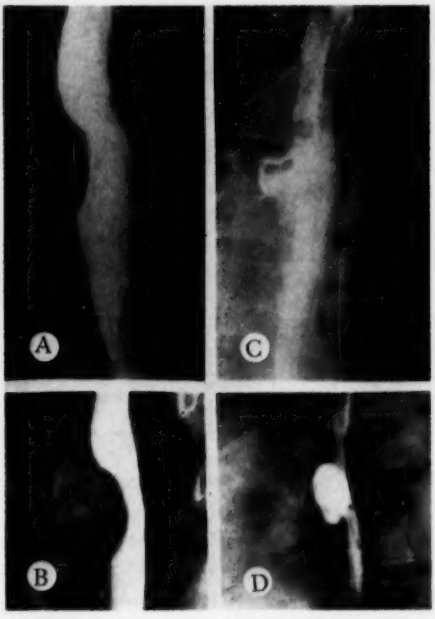


Fig. 4 (Case 4).—Development of an esophageal traction diverticulum. *A* and *B*, February, 1954. Frontal and left oblique esophagrams. A defect is evident on the right anterior wall of the middle third of the esophagus. *C* and *D*, August, 1954. Similar views. The defect has been replaced by a diverticulum. (Reproduced with permission from *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.*[80])

examination was entirely negative, as were routine laboratory studies.

An upper gastrointestinal series, performed on Feb. 4, 1954, revealed a small extrinsic defect on the right anterior wall of the esophagus at its middle third (Fig. 4*A* and *B*). It moved with the esophagus on swallowing and did not change in size or shape with alteration of the intrathoracic pressure. A small soft-tissue mass contiguous with the defect was visible in the subcarinal region. On the chest roentgenogram the right hilar shadow appeared slightly larger and denser than the left. Anteroposterior and lateral tomograms showed a small oval shadow posterior to the right hilum and a similar shadow in the carinal region. They did not appear to contain calcium. The roentgen impression was enlargement of the right hilar and carinal lymph nodes, the latter impinging on the esophagus and probably attached to its wall.

Cultures and guinea pig inoculations of gastric washings were repeatedly negative for tubercle bacilli. Histoplasmin skin test was positive, but the complement-fixation test for histoplasmosis was negative. Serum protein determinations were normal.

The symptoms improved rapidly and entirely disappeared by the middle of February. Reexamination of the esophagus, in March, 1954, showed the defect to be much smaller. The hilar and carinal densities were no longer visible. In August, the esophageal imprint had receded completely. Instead, there was now a traction diverticulum at the exact site of the original defect (Fig. 4*C* and *D*). No calcium was identified in the soft tissues adjacent to the diverticulum. The patient has remained well except for a mild transient recurrence of dysphagia in 1957.

Comment.—The evidence that histoplasmosis was the cause of this patient's lymphadenopathy, though admittedly meager, rests on the presence of a positive histoplasmin skin test six months after he first entered the endemic area and on a long-standing positive tuberculin test. The negative complement-fixation test does not rule out histoplasmosis, since the procedure was performed on only one occasion and the timing may not have been propitious. In fact, negative serological tests are not rare in active histoplasmosis.

That fungus diseases can cause lymphadenopathy with secondary traction diverticulum of the esophagus is demonstrated by an almost identical case. This young woman also complained of dysphagia, and an intramural defect of the middle third of the esophagus was demonstrated radiologically. At operation an enlarged lymph node was found adherent to the esophagus and to the adjacent bronchus and lung. Biopsy revealed granulomatous inflammation. Gridley and Grocott stains of tissue sections revealed a fungus morphologically consistent with Cryptococcus neoformans (Torula) but which did not grow on appropriate culture media. Examination of the esophagus six months later revealed a traction diverticulum at the site of the former defect.

We are at present following two additional cases in which mild tracheobronchial lymph node enlargement developed during a subacute respiratory illness, resulting in a similar impingement upon the esophagus. In both, positive skin and complement-fixation tests for histoplasmosis were obtained. To date, 12 months after the original exam-

ination in one case and 6 months, in the other,† esophageal diverticula have not developed.

It should be noted that we have made it a rule to examine the esophagus with barium for mediastinal lymph node enlargement in all patients with slowly resolving pneumonia, as well as in those with a dense or enlarged hilum. When such nodal enlargement is demonstrated—a not infrequent event—the patient is studied not only for cancer and tuberculosis but also for histoplasmosis. In the last two cases cited above, this procedure led to the discovery of the positive complement-fixation tests.

There are several additional intrathoracic roentgen patterns which may be caused by histoplasmosis. However, because the benign nature of the disease has precluded lung biopsy and because serological evidence has not been forthcoming, we do not have any verified cases. Since these patterns are neither rare nor of mere academic interest, it appears worth while to describe them and to speculate upon the evidence for considering them manifestations of histoplasmosis.

Multiple Histoplasmomas

We have encountered five asymptomatic patients in whom many large nodules, measuring up to 3 cm. in diameter, were discovered on the chest roentgenogram (Fig. 5). In each instance some of the nodules appeared to contain calcium, although tomography was at times necessary for its demonstration. On prolonged observation, the nodules remained stationary in size in three patients and became smaller in two.

While metastatic neoplasm in the lung may, on rare occasions, contain calcium, the nodules show progressive enlargement. We have seen this in metastases from thyroid cancer and from papillary cystadenocarcinoma of the ovary, and it has been reported

† In one of these patients a traction diverticulum has appeared (18 months after the original examination).

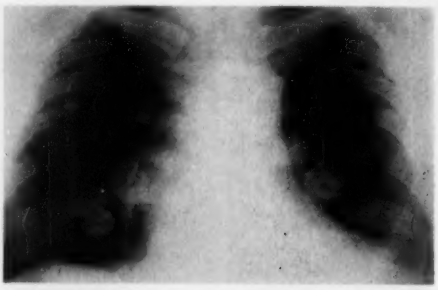


Fig. 5 (Courtesy of Dr. Maurice Walsh).—Multiple histoplasmomas? There is a central calcification in the large nodule overlying the lower right hilum and a suggestion of calcium in several other nodules. The appearance has not changed for three years. (Reproduced with permission from *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.*[80])

from osteogenic sarcoma and other primary tumors. We have also encountered a case with slowly enlarging pulmonary nodules, many with central calcification, in which tubercle bacilli were isolated from a lung biopsy specimen. However, Peabody[14] described a case with this multinodular pattern in which H. capsulatum was demonstrated on stained tissue sections of a resected nodule.

All five of our cases had positive histoplasmin skin tests, and three had negative tuberculin tests. A complement-fixation test was performed in only one case, and it was negative. The high correlation between pulmonary calcification and histoplasmosis in this section of the country, the similarity of the roentgen characteristics of the individual lesions to those of proved solitary histoplasmomas, and the resemblance to Peabody's case make it seem reasonable that at least some of these cases represent histoplasmosis.

Middle Lobe Syndrome

The term *middle lobe syndrome* is widely employed to signify long-standing collapse of the right middle lobe and the symptoms and signs resulting therefrom. The collapse is usually attributed to compression of the lobar bronchus by chronic inflammatory changes in the adjacent lymph nodes. The term itself is, of course, a misnomer, since

almost any lobar or segmental bronchus may, on occasion, be similarly affected. Moreover, other mechanisms than chronic lymphadenitis can produce identical clinical and roentgen signs.[27]

In the endemic area histoplasmosis is very likely the commonest cause of the lymphadenitis underlying this chronic collapse. While we have no unequivocally proved example in our own material, H. capsulatum has been demonstrated in such cases by others.[14,28,29] A number of our patients with chronic obstructive segmental or lobar collapse have shown bits of calcium adjacent to the occluded bronchus, and in this part of the country most intrathoracic calcifications are caused by histoplasmosis. Our experience with broncholithiasis, cited above, also lends support to the belief that the middle lobe syndrome is usually caused by long-standing histoplasmic lymphadenitis.

Similar reasoning may be applicable to the rare instances of chronic superior vena caval obstruction resulting from fibrous or calcific mediastinitis. We have recently seen an example of this syndrome, in more acute form, in which H. capsulatum was demonstrated in tissue sections obtained from a resected lung lesion adjacent to a large inflammatory lymph node which impinged on the superior vena cava.

In Cincinnati, the incidence of positive histoplasmin skin reactors approximates 80% of the total adult population. Two-thirds of the pulmonary and mediastinal calcifications found at autopsy have been shown on tissue sections to contain organisms morphologically identical with the yeast form of H. capsulatum.[25] It stands to reason, then, that in endemic areas traction diverticulum of the esophagus, broncholithiasis, chronic pulmonary collapse, and fibrocalcific mediastinitis with superior vena caval syndrome represents sequelae of histoplasmosis more often than of tuberculosis.

Summary and Conclusions

Histoplasmosis has become increasingly prominent as a cause of intrathoracic pathology, chiefly because of a greater alertness to its presence. The variety of intrathoracic roentgen patterns encountered in this disease is also increasing as experience accumulates. The present report deals with some less familiar roentgen manifestations of histoplasmosis, including the fibrocavitary form, enlarging histoplasmoma, large multinodular lesions, and certain sequelae of long-standing histoplasmic lymphadenitis, such as broncholithiasis, traction diverticulum of the esophagus, the middle lobe syndrome, and superior vena caval obstruction. In the endemic area the disease must be given serious consideration in all instances in which a diagnosis of pulmonary tuberculosis was formerly entertained.

Drs. Gerald Baum, I. Leonard Bernstein, Henry Felson, Herman J. Nimitz, Hans Plaut, Jan Schwarz, Maurice Walsh, and John T. Wilson gave permission for use of their case material.

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The Varied Clinical Manifestations of Coxsackie Virus Infections

Observations and Comments on an Outbreak in California

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Since the discovery of the prototype Coxsackie viruses by Dalldorf and Sickles, in 1948,[1] the existence of a number of additional immunologically different types has been uncovered. The known Coxsackie viruses have been placed in two different groups on the basis of histopathological changes produced in the mouse. At the present time, there are at least 19 immunologically different viruses within Group A and 5 immunologically different types within Group B.

The viruses of the Coxsackie family have a ubiquitous distribution, and their recovery from the stools of normal persons, or at least from persons with no objective or subjective evidence of illness, is by no means unusual. However, the accumulating evidence over the past few years has served to establish the causal relationship of the Coxsackie viruses to certain diseases. Thus, it is now generally accepted that viruses in the Coxsackie A group are the etiologic agents of herpangina and are probably involved in the causation of several other illnesses. Viruses in the Coxsackie B group have been established as the etiologic agents of epidemic pleurodynia (Bornholm disease), aseptic meningitis, and, more recently, myocarditis in the newborn.

We wish here to outline very broadly certain general epidemiologic and clinical observations incident to a large outbreak of Coxsackie virus infection in California, which was first recognized in and around Shasta County in the summer and fall of 1956. The outbreak was primarily one of pleurodynia, but cases of aseptic meningitis and, as will be described herein, of pericarditis and pleural effusion were also encountered. Information gained from the usual morbidity-reporting channels and through personal inquiries indicated that Coxsackie virus infections were occurring in many areas of the state. Virological examinations of material from patients from these various communities indicated that the infections were due primarily to Coxsackie virus Type B-5. So far as we are aware, this is the first time that this immunologic type has been incriminated in an outbreak of epidemic pleurodynia. In addition to some comments on this outbreak of pleurodynia, we wish to present evidence incriminating a Coxsackie virus as an etiologic agent in acute benign pericarditis.

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Epidemic Pleurodynia (Bornholm Disease)

This clinical syndrome was first described by Daae[2] and Homann,[3] in Norway, in 1872, and by Finsen,[4] in Iceland, in 1874. Finsen, whose observations date from 1856, referred to the disease as pleurodynia, but the numerous outbreaks of this disease recorded since the original descriptions have

led to its designation by a variety of names. Thus, the disease has received geographical names, such as Skien disease, Bamle disease, Drangedal disease, and Bornholm disease, or somewhat more descriptive names, such as epidemic pleurodynia, epidemic myalgia, devil's grippe, epidemic diaphragmatic spasm, and epidemic benign pleurisy. The name Bornholm disease (after the Danish island in the Baltic Sea) was used by Sylvest[5] in several publications prior to the appearance of his famous monograph, in 1934. Since the disease in the United States is perhaps best known by the names "epidemic pleurodynia" and "Bornholm disease," both designations will be used here.

The epidemic of pleurodynia which occurred in northern California in 1956 did not differ remarkably in its epidemiologic pattern from the outbreaks described by other workers (Sylvest[5]; Pickles,[6] and Huebner et al.[7]). The disease characteristically occurs in epidemic form and usually in the summer and fall. This was true in California, where well over 500 cases are estimated to have occurred in Shasta County and environs alone during the late summer and fall months. Most of the cases occurred in urban areas, and the incidence of infection was greatest in children and young adults; the age distribution of 60 patients on whom adequate clinical or laboratory data, or both, were available for study, is shown in Table 1.* It will be noted that one-half of the cases in this study group were persons from 0-19 years of age and that three-fourths occurred in persons from 0-29 years of age. There was no difference in the sex incidence of

TABLE 1.—*Age Distribution of Sixty Cases of Epidemic Pleurodynia*

Age Group	Patients, No.
0-9	22
10-19	8
20-29	17
30-39	8
40-49	2
50-59	2
60-64	1

the disease. The occurrence of multiple cases in a family was not unusual, and in some instances all, or nearly all, members of the family became ill. Multiple cases occurred almost simultaneously, or they followed each other in rapid succession with intervals of several days between cases. Clinically inapparent infections also occurred, as shown by recovery of virus from the stools and a rise in antibody titer in non-ill familial contacts.

The incubation period is about two to four days. The onset is generally sudden and is frequently heralded by sudden severe thoracic pain, usually at the level of the diaphragm, and frequently without prodromal signs. The pains are severe and lancinating and occur unilaterally or bilaterally. Not infrequently they may be confused with the pain attendant upon a myocardial infarction. Coughing, sneezing, sobbing, laughing, and similar exertions aggravate the pain, and not infrequently even the act of normal breathing severely enhances it. In some persons, especially children, the pains are abdominal, tending toward the epigastrium and eliciting a protective splinting of the abdominal musculature. Pain and tenderness of the muscles in the trunk and extremities may also occur. With the onset of pain, i. e., the illness, the patient complains of generalized aches and headache, usually frontal; the temperature rises, frequently to 100-101 F and occasionally as high as 105 F, and is accompanied by a rapid pulse. Pain and fever usually last one to two days and then subside. The patient may remain asymptomatic for several days, after which there

* Of the 60 patients with clear-cut clinical evidence of pleurodynia, laboratory diagnosis of Coxsackie virus infection was made in 36 by isolation of the virus from the stools and/or by a rise in complement-fixing antibody titer or by a high stationary antibody titer to Coxsackie virus. In the remaining 24 patients, the clinical picture was so similar to that of other patients in the outbreak in whom laboratory diagnosis was positive that they were included despite the fact that no laboratory tests had been done.

may be a recurrence of pain and fever. This biphasic type of illness is not uncommon. The total duration of illness has been reported to range from 1-20 days, depending upon the number of relapses.[7]

The following history illustrates the type of cases seen with manifestations of pleurodynia.

CASE 1.—This patient was a 24-year-old white office nurse, who had been exposed to at least three known cases of acute pleurodynia in the week prior to onset of her symptoms. The disease was ushered in by marked fatigue and a loss of appetite. She was awakened during the night by a sharp knife-like chest pain which she described as the severest she had ever experienced. The pains were paroxysmal, came suddenly, and lasted from 30-90 seconds. The pains occurred intermittently throughout the night and were aggravated by respiration. By morning the acute pain had ceased but there was a residual tenderness in the area where the pains had occurred. During the night, the patient's temperature had risen to 101 F; subsequently there was a sudden drop in temperature, accompanied by a profuse diaphoresis. During the following 24 hours, however, there was a recurrence of the vise-like pains, which were described as migrating about the chest and epigastrium. The patient also complained of marked fatigue and occipital headache.

Pain was attenuated by the use of codeine and acetylsalicylic acid, and, except for an inordinate degree of weakness, the patient was afebrile and completely free of symptoms in 72 hours.

A laboratory diagnosis of Coxsackie-virus infection was made by isolation of Type B-5 Coxsackie virus from the patient's stools and by the finding that a rise in complement-fixing antibody titer to this same Coxsackie virus type had occurred during the course of her illness (the titer rose from 1:8 in the acute-phase blood specimen to 1:128 in the convalescent-phase blood specimen).

The frequency distribution of symptoms noted in the 60 patients on whom comprehensive observations were made is shown in Table 2. It is of interest to note that nearly one-half of the patients experienced abdominal pain, with or without chest pain. Vomiting, coughing, or pharyngeal inflammation have been described as rare or infrequent in epidemic pleurodynia. Among the persons listed in Table 2 cough was unusual, but it will be observed that sore throat was a complaint in about 25% of the patients and that nausea or vomiting was encountered in 31%. A similar high incidence of nausea and vomiting has been reported by Johnsson.[8] Throat cultures were taken on 22 patients; nothing remarkable was found. The blood and urinary findings were within normal limits.

TABLE 2.—*Incidence of Symptoms in Sixty Patients with Epidemic Pleurodynia*

Symptoms	Patients, No.	% of Total Group
Fever	56	93
Chest pain	44	73
Headache	35	58
Myalgia	31	51
Abd. pain	29	49
Nausea or vomiting	19	31
Sore throat	14	23
Stiff neck	14	23

Some of the conditions which may be mistaken for pleurodynia are appendicitis, pancreatitis, common bile duct obstruction, acute cholecystitis, perforated peptic ulcer, coronary insufficiency, pneumonia, and pulmonary infarction. Indeed, a differential diagnosis at times is so difficult that it led Pickles[9] to remark, "For a relatively innocuous illness with no death rate, it is remarkably successful as a mimic of serious disease, both abdominal and thoracic, and unless the syndrome is very clearly defined, many of these sufferers will find their way to the operating table, as it is certain they have done in the past."

Complications of pleurodynia appear to be rare[5] but include orchitis, pleurisy, and, rarely, meningitis. Jamieson and Prinsley[10] mention orchitis as the commonest complication encountered by them, and Morrison and Baird[11] stress the importance of orchitis as a complication. The latter authors state that Bornholm disease (i. e., Coxsackie virus infection) should be considered in cases of epididymo-orchitis of undetermined etiology and especially if this condition appears in epidemic form. In the experience encompassed by this report, we encountered one instance of orchitis among the 60 persons described above and in two other persons outside this group. Pleurisy as a complication was not uncommon.

This situation with respect to meningitis is of interest. In the present study we encountered many cases of essentially pure pleurodynia, as well as a small number of clear-cut examples of the aseptic meningitis syndrome; in between were a number of patients in whom evidence of meningeal involvement, manifested by severe headache and stiff neck, appeared concomitantly with the basic clinical picture of pleurodynia or developed shortly thereafter. To what extent meningeal involvement is to be regarded as a complication of epidemic pleurodynia and to what extent a primary manifestation of infection with a Coxsackie virus remains to be more clearly delineated.

Aseptic Meningitis Due to Coxsackie Virus

An association between aseptic meningitis and Bornholm disease was remarked upon by Lindberg,[12] in 1936, and again some years later (1949) by Gsell.[13] Johnsson[14] mentions several patients with the symptoms and signs of both pleurodynia and aseptic meningitis.

The supervention of a meningeal component upon a pleurodyneal picture is illustrated by the following instances.

Case 2.—The patient, a 9-year-old white girl, suffered from an episode of fever, muscular aches, and chest and abdominal pains. Placed on bed rest, she appeared to be recovering gradually, but five days after the onset of illness she developed a fever (temperature of 103 F), became flushed, and was found to have some stiffness of the neck, back, and hamstring muscles. She complained vigorously of malaise and headache. Spinal fluid examination showed the presence of 280 cells, of which 70% were lymphocytes and 30% were polymorphonuclear leukocytes; the protein was 30 mg. %, and the sugar was 70 mg. %. No organisms were seen on microscopic examination, and bacteriologic cultures of the fluid proved negative. The patient received only acetylsalicylic acid, and in 36 hours her temperature returned to normal. The muscle stiffness disappeared, and she was clinically well. When examined one month later, she showed no residual weakness.

A laboratory diagnosis of Coxsackie virus infection was made by isolation of Coxsackie virus Type B-5 from the stools, together with very high levels (titer of 1:128 or greater) of complement-fixing antibody to this same virus type. Inability to detect a rise in antibody titer is attributed to the fact that the first blood specimen was taken during the early recovery rather than in the acute phase of the illness.

Cases 3 and 4.—Case 3 was a 3-year-old white girl. Her presenting complaint was headache, pain in the eyes, and chest pain. On the following day, the temperature was 102 F and a frank meningismus had developed. The spinal fluid cell count was 389 white cells, of which 91% were polymorphonuclear leukocytes; the fluid was negative for bacteria by smear and by culture. The child was hospitalized and placed on antibiotic therapy. (The existing antibiotics have no effect on Coxsackie virus.) Recovery was essentially complete within a week.

Simultaneously with the onset of illness in the baby, her mother (Case 4) developed severe pains in the thoracic and upper abdominal regions, accompanied by severe headache and marked neck pain. Her temperature was 102 F. Over the next seven days the temperature gradually returned to normal, accompanied by amelioration and subsequent disappearance of the pain and other symptoms.

Blood specimens were obtained from mother and child during the acute phase of the illness, and a second blood specimen was obtained from each patient approximately three weeks after the first. Both patients showed a diagnostically significant rise in complement-fixing antibody to Coxsackie virus Type B-5; the baby's antibody titer to this type rose from 1:16 to 1:64, and the mother's titer rose from 1:8 to 1:128.

The subject of aseptic meningitis of Coxsackie virus etiology is well covered by a number of authors,[15-17] and additional description of the clinical picture is not warranted here. We wish at this point only to mention again that in the California episode we encountered not only patients with a pure aseptic meningitis picture and those with an essentially pure pleurodyneal picture but also a number of patients in whom the clinical picture was a composite of these two. As already mentioned, Lindberg,[12] Gsell,[13] and Johnsson[14] noted the occurrence of aseptic meningitis with Bornholm disease. Gabinus et al.[18] also described an outbreak in which they encountered pleurodynia without meningitis, meningitis without pleurodynia, and pleurodynia and meningitis combined. On the basis of their data and knowledge available at that time,

they suggested, "It might even be reasonable to ask whether the meningitis might not be a separate etiological entity"; they concluded, however, that their findings did not justify the assumption that the pleurodynia and the meningitis were caused by two separate agents. Evidence in favor of a single etiology was later reported by Johnsson,[14] who recovered a Coxsackie B virus from the spinal fluid of a patient with typical pleurodynia and meningitis; subsequently, four cases of laboratory infection with this strain occurred, the symptoms being pleurodyneal in three and meningitic without myalgia in one.

Monkey-kidney-cell cultures and one-day-old mice were used throughout these studies for virus isolation and identification purposes. Except for several cases of poliomyelitis, paralytic or nonparalytic, from whom poliomyelitis viruses were isolated (in tissue cultures), the only agent recovered in the Shasta County area was Type B-5 Coxsackie virus. This was virtually the only Coxsackie type recovered in 1956 from patients in other parts of the state also. Early in the outbreak patients with meningeal involvement were considered clinically to have nonparalytic poliomyelitis, but the virus isolation studies soon indicated that the poliomyelitis viruses were not the incitants of the C. N. S. disease being encountered. Furthermore, serologic tests ruled out the viruses of mumps, herpes simplex, Western equine encephalitis, St. Louis encephalitis, and lymphocytic choriomeningitis as etiologically responsible. Thus, regardless of whether the patient showed a clinical picture of pleurodynia, meningitis, pleurodynia-meningitis, or even pericarditis (see below), laboratory tests almost invariably pointed to Type B-5 Coxsackie virus as the etiologic agent.

Cardiac Involvement by Coxsackie Viruses

Myocarditis.—It is now generally recognized that certain infectious diseases, and especially those of viral etiology, may be attended by the development of inflammatory interstitial lesions of the myocardium.[19,20] The possibility that Coxsackie viruses might be the incitants in focal myocarditis was suggested by Stoeber,[21] in his report on the postmortem findings in "epidemic myocarditis" of infants. In 1955, Montgomery et al.[22] described the occurrence of an acute febrile illness in three newborn infants in a nursing home; in one instance the illness terminated fatally. The cause of death was an acute and extensive focal myocarditis. Type B-4 Coxsackie virus was recovered from the stools and intestinal contents of the infant who died and from the stools of one of the two surviving infants. Shortly thereafter, Javett et al.[23] reported that during a period when Bornholm disease was present a number of newborn infants developed a biphasic type of illness—the first phase consisted of diarrhea, followed after an interval of several days by the second phase, a fulminating illness that ended in a circulatory collapse. Six of the ten babies affected died. The outstanding lesion in the three fatal cases that were examined post mortem was a patchy myocarditis. A virus, classified as Coxsackie Group B on the basis of histopathologic changes produced in baby mice, was isolated from the brains of two of the fatal cases and from the stools of two of the infants who recovered. One of the latter viruses was later identified as a Coxsackie virus Type B-3. In an addendum to their paper, Javett et al.[23] mention isolation of a Group B Coxsackie virus from the heart muscle of a newborn infant who died shortly after developing symptoms and signs of myocarditis; histologic sections showed myocardial lesions similar to those described for the patients presented in the main body of their paper. Van Creveld and De Jager[24] described four cases of myocarditis in newborn children which occurred during an epidemic of pleurodynia. The clinical diagnosis was confirmed by postmortem examination, which revealed the presence of an interstitial myocarditis. A Type B-4 Coxsackie virus was isolated

from the heart muscle of these infants.[25] Kibrick and Benirschke [26] recovered a Type B-3 Coxsackie virus from the spinal cord of a newborn infant, who was presumably infected *in utero* and died with an acute myocarditis and meningoencephalitis; in an addendum, isolation of a Type B-4 virus from the myocardium of another infant is mentioned. Kagan and Bernkopf [27] reported on seven cases of myocarditis in children during an outbreak of respiratory disease; a Coxsackie virus was isolated from the myocardium of two fatal cases and from lung tissue and blood of a third.

Although we were aware that Coxsackie virus may produce myocarditis in infants and made efforts to detect the occurrence of such cases, we did not locate any. In view of the large population affected by the outbreak of Coxsackie virus infections, cases of myocarditis presumably would have been detected had they occurred; the fact that we encountered none, however, does not rule out the possibility that instances of myocarditis did occur but escaped our attention.

Pericarditis.—Acute benign pericarditis is generally regarded as a clinical syndrome of unknown etiology, although, as in the case of myocarditis, a diversity of agents has been suspected. Again, as in the case of myocarditis, there appears to be some relationship between benign pericarditis and infectious disease, and especially diseases of viral etiology.[28,29] With respect to epidemic pleurodynia, Bing,[30] in 1933, described the occurrence of six cases of pericarditis in patients with this disease. Heckscher [31] and Finn et al.[32] recorded single instances of pericarditis associated with epidemic pleurodynia, and Aagaard and Jensen [33] described seven cases, five of which occurred during an epidemic of Bornholm disease. Cumulatively, these observations suggest, but do not prove, an etiologic relationship between Coxsackie virus infection manifested in the form of Bornholm disease and the occurrence of pericarditis. Additional evidence incriminating Coxsackie viruses as a cause of benign pericarditis was obtained during the course of our studies. Seven cases of pericarditis associated with pleurodynia came to our attention. Detailed information is presented here on two of these patients, and the pertinent information on all seven is summarized in Table 3.

CASE 5.—This patient, a 22-year-old-white man, developed evidence of acute respiratory infection on Oct. 1, 1956. During the next 48 hours pain appeared in the left chest and upper abdomen, became increasingly severe, and was aggravated by respiration. Vague generalized malaise was present, but cough, headache, and chills were absent.

TABLE 3.—*Results of Virus Isolation Attempts and Coxsackie B-5 Antibody Determinations in Seven Patients with Pericarditis Consequent to Pleurodynia* *

Patient	Age	Sex	Clinical Picture	Virus Isolation from Stool		C-F Antibody Titer to Type B-5 Coxsackie Virus		
				Monkey-Kidney-Cell Cultures	1-Day-Old Mice	Acute Phase	Recovery Phase	Convalescent Phase
A (Case 5 in text)	22	M	Pericarditis	Cox. B-5	N. D. †	<1:8	1:16	1:32
B	21	M	Pericarditis; pleural effusion	N. D.	N. D.	1:64		1:256
C	5	M	Pericarditis; pleural effusion	Neg.	Neg.			1:512
D	9	M	Pericarditis	N. D.	N. D.		1:32	1:32
E	30	M	Pericarditis	Neg.	Neg.			1:256 or >
F	31	M	Pericarditis	N. D.	N. D.			1:128
G (Case 6 in text)	41	M	Pericarditis; pleural effusion	N. D.	N. D.	1:64 ‡	1:64	1:64

* Tests for poliomyelitis viruses in the stools of these patients were negative in all instances.

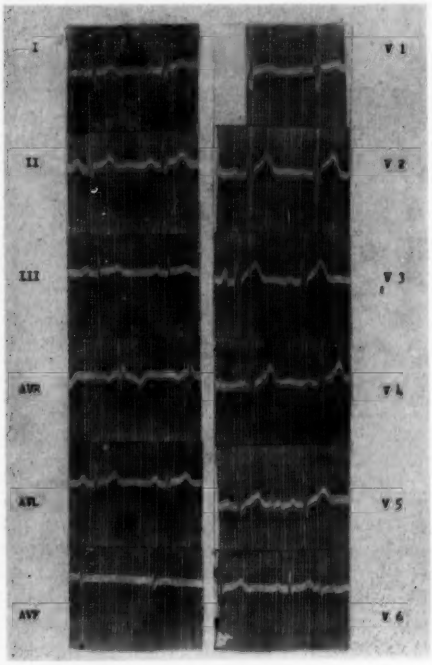
† N. D. indicates not done (no specimens available for test).

‡ Date of onset of illness in this patient uncertain.

The patient was hospitalized on the second day of illness. The physical examination, including special attention to the cardiorespiratory system, was essentially negative. The blood and urinary findings were within normal limits. A roentgenogram of the chest revealed no significant abnormalities, and a subsequent film taken Oct. 11, 1956, was also considered to show nothing remarkable. The patient was placed on acetylsalicylic acid and codeine medication, which served to alleviate the pain markedly.

On the third hospital day, the patient's temperature rose to 103.4 F, but it returned to normal within 24 hours. The fever was accompanied by an increase in the pulse rate to 105. The following day, he complained of retrosternal discomfort which was associated with changes in body position. A faint friction rub was heard at the base of the heart on the fifth hospital day, and on the following day, it was loud and harsh, suggestive of pericarditis. Minimal exertion, such as sitting up, would accelerate the pulse rate. Electrocardiographic findings were reported as compatible with pericarditis (Figs. 1-3). On the ninth hospital day (four days after onset of friction rub), the patient's pain began to diminish and the electrocardiographic pattern began to revert to normal.

Fig. 1 (Case 5).—Oct. 8, 1956. Slight to moderate elevation of the ST segments in standard leads and aV_F.



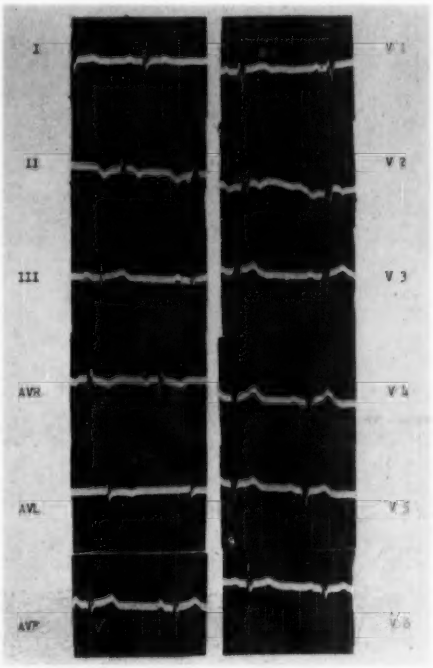


Fig. 2 (Case 5).—Oct. 16, 1956. Lowering of T-waves in right precordial leads, which are assuming a diphasic character.

The patient was discharged as asymptomatic on the 14th hospital day.

A Coxsackie virus Type B-5 was isolated from the stools, and a rise in complement-fixing antibody from 1:8 to 1:32 to this type was demonstrable when acute- and convalescent-phase blood specimens were examined.

Case 6.—This 41-year-old white man developed dyspnea, right chest pain, and intermittent chills and fever about Sept. 9, 1956. On Sept. 23, pain suddenly became severer and he was hospitalized. Examination on admission revealed a well-developed well-nourished white man in moderate distress. His temperature was 102 F; pulse, 112. The chest was clear to percussion and auscultation, but splinting of the left side of the thoracic cage was noted. No murmurs were heard. The blood pressure was 100/68. Laboratory findings at that time were as follows: hemoglobin 13.6 gm.; RBC 5,180,000; WBC 12,800, with differential count showing neutrophils 58%, lymphocytes 39%, monocytes 1%; urine: not remarkable; erythrocyte sedimentation rate 31 mm. Wintrobe (corrected); antistreptolysin titer 50 Todd units; heterophil agglutination tests negative; complement-fixation tests for Q-fever and psittacosis negative; skin tests for Coccidiodes and tuberculosis negative. Blood cultures taken on

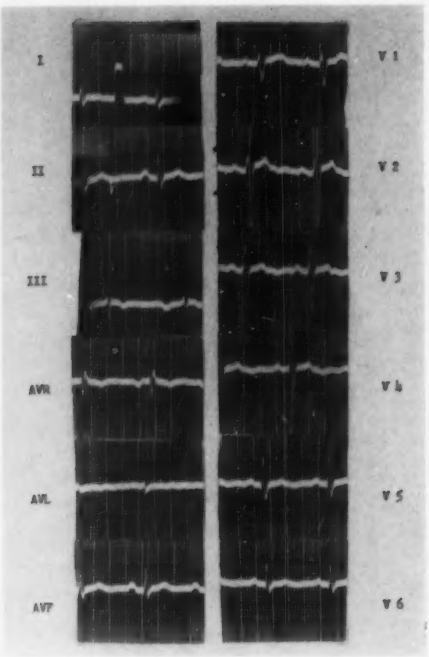


Fig. 3 (Case 5).—Oct. 23, 1956. Elevated ST has returned to base line but minor abnormalities of the T-waves persist.

three different occasions yielded no bacterial growth.

A roentgenogram of the chest revealed a pneumonic process in the basal segment of the left lower lobe and a small effusion in the posterior gutter. An electrocardiogram (Fig. 4) on Sept. 25 showed changes suggestive of pericarditis. The patient's temperature fluctuated between 99 F and 101 F for five days; then it gradually returned to normal, where it remained for five days, and then began to spike from 100 F to 102 F daily until Oct. 11. During this interval the patient frequently complained of pains throughout the entire chest and also developed a cough. Rales were heard in the right lower lobe, and a pleuropericardial friction rub was heard. The pain became severe enough to require heavy analgesia. Electrocardiograms continued to show small changes (Fig. 5) interpreted as evidence of pericarditis, and an x-ray film at this time showed a right pleural effusion. On Oct. 13 a thoracentesis was performed, and 275 cc. of thick red fluid was removed. The aspirate was bacteriologically sterile on the usual culture media, and guinea pigs given inoculations with the material showed no evidence of tuberculous infection at the end of six weeks. During the acute stage of this illness the patient developed a moderate

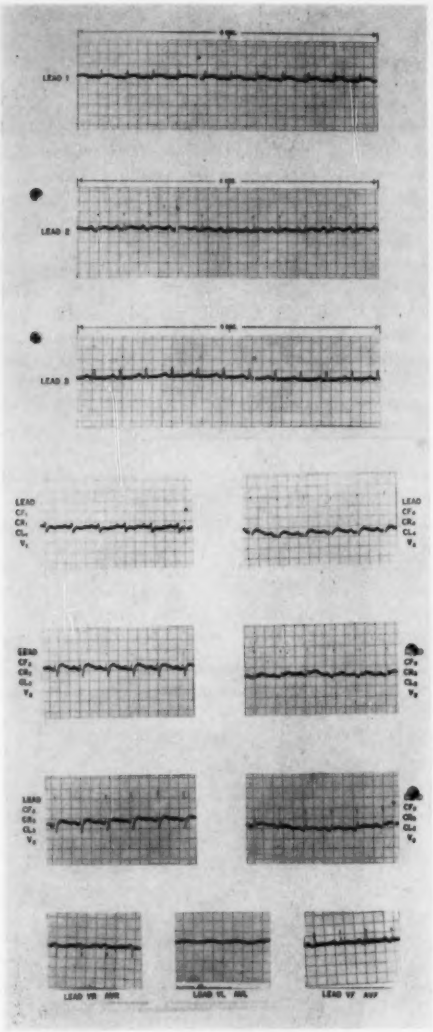


Fig. 4 (Case 6).—Sept. 25, 1956. Abnormalities of the ST-T segments in all leads with elevation of ST I, II, V_2-V_6. T-waves diphasic, flat, or inverted.

tachycardia and a pulse pressure between 30 and 40 mm. was a rather constant finding.

The patient's temperature gradually returned to normal, and the friction rub, as well as the subjective symptoms, disappeared. Electrocardiogram tracings began to revert to a normal pattern (Fig. 6). A chest roentgenogram (Fig. 7) on Nov. 16, 1956, showed a moderate increase in the pleural effusion of the right side and a recurrence of the effusion in the left pleural space.

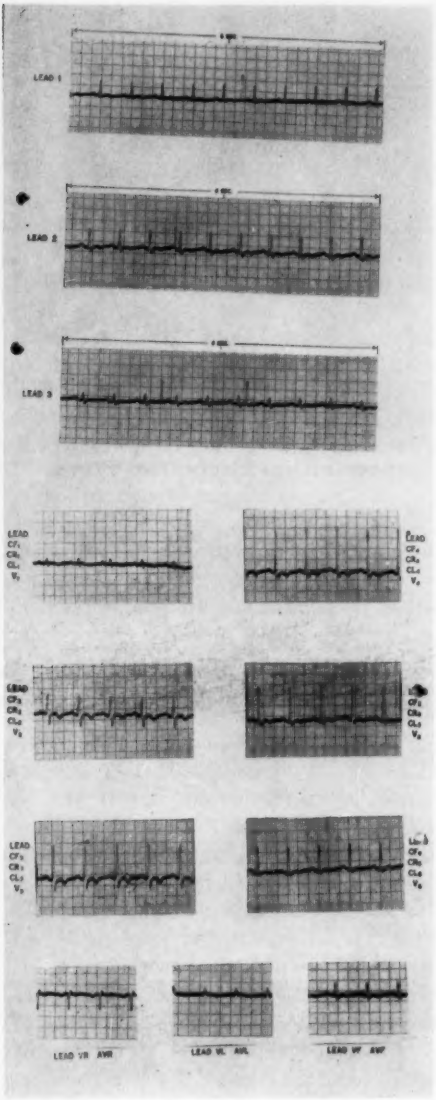


Fig. 5 (Case 6).—Oct. 8, 1956. Inversion of some T-waves with some coving in limb leads and precordial leads.

As the patient was not seen until very late in his disease, no stool specimens or acute-phase blood serum was available for examination. However, serial blood specimens, the last taken two months after the presumed date of onset of symptoms, all showed complement-fixing antibody titers of 1:64 to Type B-5 Coxsackie virus.

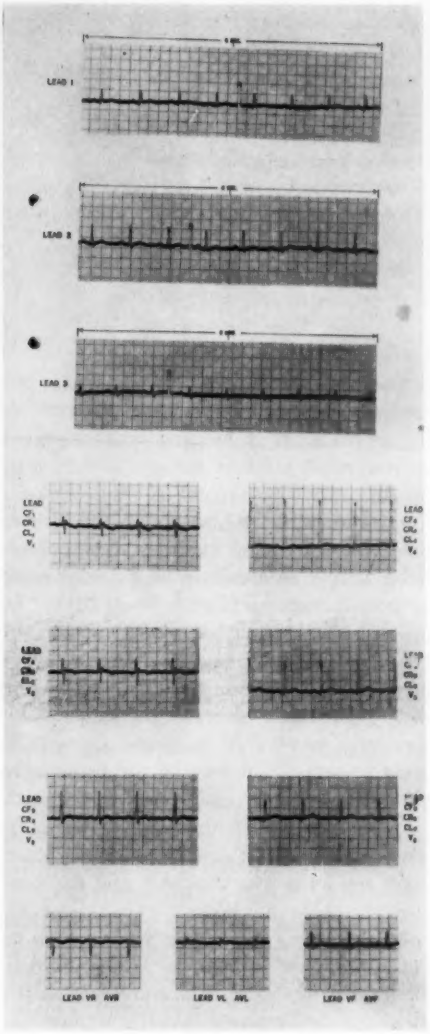


Fig. 6 (Case 6).—Oct. 25, 1956. Significant reversion toward a more normal pattern with some persistence of abnormalities of T-waves in some precordial leads.

Table 3 lists seven patients, including Cases 5 and 6 described above, who developed clinical signs and symptoms of pericarditis consequent to an attack of pleurodynia. This highly suggestive cause-and-effect relationship found support in the results of etiologic studies. Thus, as is shown for Patient A listed in Table 3, whose clinical course was described above

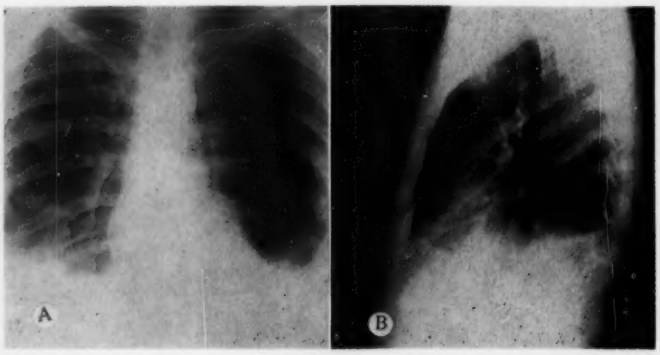


Fig. 7 (Case 6).—Nov. 16, 1956. Pleural effusion. *A*, recurrence. *B*, moderate increase.

as Case 5, a Coxsackie B-5 virus was isolated from the stools, and complement-fixing antibody to this virus type appeared and increased in titer during the course of the illness. With respect to Patient B, a diagnostically significant, i. e., fourfold, rise in complement-fixing antibody titer to Coxsackie B-5 virus occurred during the illness, the titer increasing from 1:64 to 1:256. In the remaining five cases, virus isolation attempts were either negative in monkey-kidney-cell cultures, in one-day-old suckling mice, or in both or were not undertaken. However, in all five instances appreciable levels of complement-fixing antibody were encountered. The significance of the antibody in Patients D and G may be questioned, since, in the former, no acute-phase blood specimen was available and the convalescent-phase antibody titer was not remarkably high (although it was as high as that for Patient A); in the latter, the date of onset of illness was uncertain and so the presumed "acute-phase" blood specimen had an antibody level as high as that found in the convalescent-phase blood. In the remaining three cases, rather high complement-fixing antibody titers to the Coxsackie B-5 virus were found in the convalescent-phase sera and probably are significant in view of the fact that the outbreak was due to Coxsackie B-5 virus.

The high antibody levels encountered during convalescence are similar to those recently reported by others. While this paper was in preparation, there appeared the reports of Fletcher and Brennan[34] and of Weinstein,[35] pointing to the possible etiologic role of Coxsackie viruses in acute benign pericarditis. Fletcher and Brennan[34] described the occurrence of pericarditis in a 28-year-old woman whose initial illness was pleurodynia; the patient's serum, when tested during convalescence, was found to contain no neutralizing antibody to any of the Coxsackie Group B viruses except Type B-4, against which the titer was 1:128, a high level. Weinstein[35] described a case of acute benign pericarditis in a 25-year-old man. A blood specimen taken during convalescence was found to have a complement-fixing antibody titer of 1:512 to Coxsackie virus Type B-5. It seems likely that a Group B Coxsackie virus was the etiologic agent in both instances. Evidence of a similar nature, implicating Coxsackie viruses, is afforded by at least three and perhaps all five of the patients in the lower portion of Table 3, but somewhat more concrete evidence is supplied in the case of the two patients presented at the top of the Table. In Patients A and B, a diagnostically significant rise in complement-fixing antibody to Coxsackie B-5 virus was encountered, and this same immunologic virus type was also recovered from the stools of one of these patients. Additional direct evidence of the causal role of Coxsackie viruses in pericarditis was recently provided by the study of Kagan and Bernkopf,[27] which came to our attention after this paper was completed; these authors re-

covered a Coxsackie B-3 virus from the pericardial fluid and the stools of a 10-month-old child with acute pericarditis.

Comment

Morbidity reports made to the state and local health officers during the late summer of 1956 revealed the occurrence of an epidemic of Bornholm disease in and around Shasta County, Calif., and the occurrence of small outbreaks of sporadic cases in various other parts of the state. Inquiries showed that, in addition to epidemic pleurodynia (Bornholm disease), there occurred a number of cases of aseptic meningitis, apparently arising as a complication of the antecedent pleurodynia, and a small number of cases of aseptic meningitis without any prior history of pleurodynia or myalgia. It is of interest that not only was clear-cut evidence obtained that a Coxsackie virus was responsible for these diverse clinical manifestations but also only a single immunologic type, namely Coxsackie B-5, was involved.

The studies summarized in this paper provide additional evidence incriminating the Group B Coxsackie viruses as the probable etiologic agents in at least some cases of acute benign pericarditis. An interesting finding is that all seven cases reported here, as well as the one described by Weinstein [35] and which we had the privilege of studying, occurred in males. This preponderance of males in the sex incidence of pericarditis has been remarked upon by others. In three of the patients described herein pleural effusion was a concomitant of pericarditis.

The experience recorded here shows rather clearly, in our estimation, that infection with a Coxsackie virus may be expressed clinically in the form of one or another of several syndromes or as a composite combining several of their major features. It is unclear why infection should express itself as a pleurodyneal affair in one patient and as a pure aseptic meningitis in another and why one patient with pleurodynia should develop a meningitis seemingly as a complication whereas another responds with an involvement of the pericardium. The question as to what the host factors might be that determine the pattern in which the infection will ultimately express itself clinically forms the basis for some interesting speculation and study. At the moment, age seems to represent one such possible factor. So far as we are aware, myocarditis due to Coxsackie virus has been reported primarily in infants, whereas pericarditis seemingly affects chiefly adults. Whether the age factor here is more apparent than real remains to be seen. Again, with respect to age, the observations of some workers [36] suggest that in some situations pleurodynia is commoner in adults than in children, whereas infection in children more commonly manifests itself as an aseptic meningitis. On this basis, the clinical pattern of an epidemic of Group B Coxsackie virus infections would be influenced or determined by the age distribution of susceptible persons within the community.[36] In a community with little or no prior exposure to Coxsackie virus, a large proportion of the susceptibles would be adults and the epidemic would be primarily one of pleurodynia. Conversely, in an area where a large part of the adult population is immune, as a consequence of prior exposure, the epidemic would involve primarily children and the "symptoms would generally be milder; myalgia and pleurodynia would not be a prominent feature." [36] Our own observations on this interesting aspect are inadequate to contribute any significant information.

Summary

Observations made during an outbreak of Coxsackie virus disease in California in 1956 are outlined and discussed in relation to the clinical findings reported by others to be associated with Coxsackie virus infections.

So far as we are aware, this is the first time that Coxsackie virus Group B, Type 5

has been reported as a cause of epidemic pleurodynia.

The Coxsackie Group B viruses have already been incriminated as a cause of myocarditis in infants. These viruses are now also incriminated as etiologically responsible for some cases of acute benign pericarditis.

The data presented in this report show that infection with a single immunologic type of Coxsackie virus, namely, Group B, Type 5, can give rise to a variety of clinical manifestations, such as epidemic pleurodynia, aseptic meningitis, pleurodynia with meningeal involvement, pericarditis, and, very probably, myocarditis.

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Cell Counts in Urine

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Addis[1,2] established the fact 30 years ago, with use of a counting chamber, that both white and red cells normally occur in urine. He found top values of 2,000,000 white cells and 400,000 red cells in the 12-hour night urine specimens of 74 apparently healthy medical students. Inasmuch as the collections averaged 352 ml., it appears that some 6,000 white cells and about 1,000 red cells may be expected per milliliter of urine in health. However, Addis' method has been found too cumbersome for general use, and his results for whole urine have seemed of limited value, since they were not correlated with simultaneous counts per hpf of the centrifuged sediment, the more familiar procedure.*

I have made a series of 500 such correlations between cell counts of the sediment prepared in the usual fashion and simultaneous cell counts of the whole urine by use of the counting chamber. It appears from the present series that Addis' figures must correspond to 1-2 white cells per hpf and to 1 red cell to every 2-3 hpf, which we have termed "occasional."

This correlation has been confirmed by cell counts in the sediments of 5,000 consecutive male and 1,000 consecutive female specimens received at the John Hancock Mutual Life Insurance Company home-office laboratory in connection with insurance applications, the female series being smaller because fewer women apply. All were ex-

Quantitative Incidence of White and Red Cells in Urine Sediments

	Male (5,000 Sediments), No. Occurrences		Female (1,000 Sediments), No. Occurrences	
Cell Count /HPF	White Cells	Red Cells	White Cells	Red Cells
0	28	3,920	2	778
Rare	2,036	325	145	50
Occ.	1,823	315	307	74
1	392	142	155	31
2	169	45	76	9
3	53	21	23	2
4	40	22	18	1
5	58	53	35	10
6	29	20	22	4
7	31	20	13	5
8	16	3	7	3
9	18	3	8	2
10	33	8	8	
11	14	1	16	
12	8	11	4	
13	22	16	18	5
14	8		5	
15	6	2	5	
16	5		4	
17	22	9	9	2
18	7		2	
19	3			
20	3			
21			1	
22	3		2	
23	4	1	4	1
24	3		1	
25	8	3	9	2
26	3		3	
27	9	4	5	3
28	5		1	
29	4		1	
30	3		2	
31				
32				
33		1	2	
34	2		2	
35	15	13	12	2
36	3		2	
37	2		1	
38	1		1	
39	1		1	
40			2	
41				
42			1	
43			1	
44	2		1	
45	8	14	8	7
46	2		2	
47	1		1	
48	1		1	
49	1			
50	3	1	5	2
Over 50	92	27	46	7

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* Fifteen milliliters of urine in a centrifuge tube are centrifuged for five minutes at 2,000 rpm; the supernatant, poured off; the sediment, shaken up, and one or two drops poured onto a slide, covered with a ⅞ in. cover glass, and examined under high dry power.

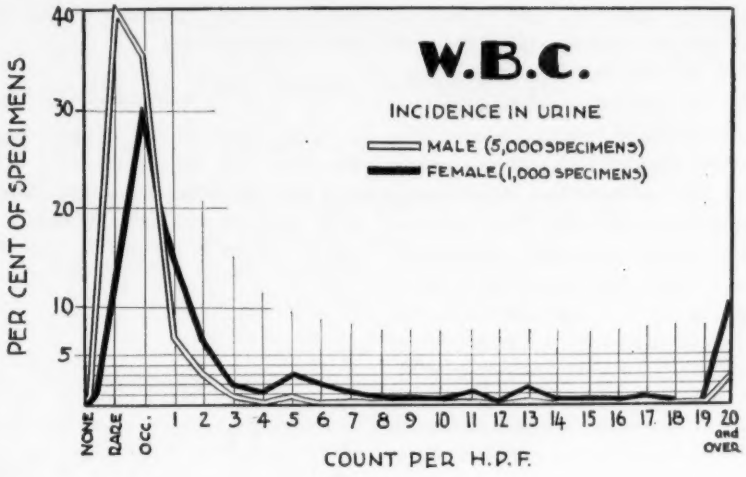

Figure 1

amined by me. None was obtained by catheter.

Insurance experience indicates that the vast majority of these specimens would have to be normal. Since clinical correlation was impossible, it was postulated that a sharp break in the pattern might mark a limit for normal. This is, of course, an actuarial approach relying on weight of evidence. And such a break does, indeed,

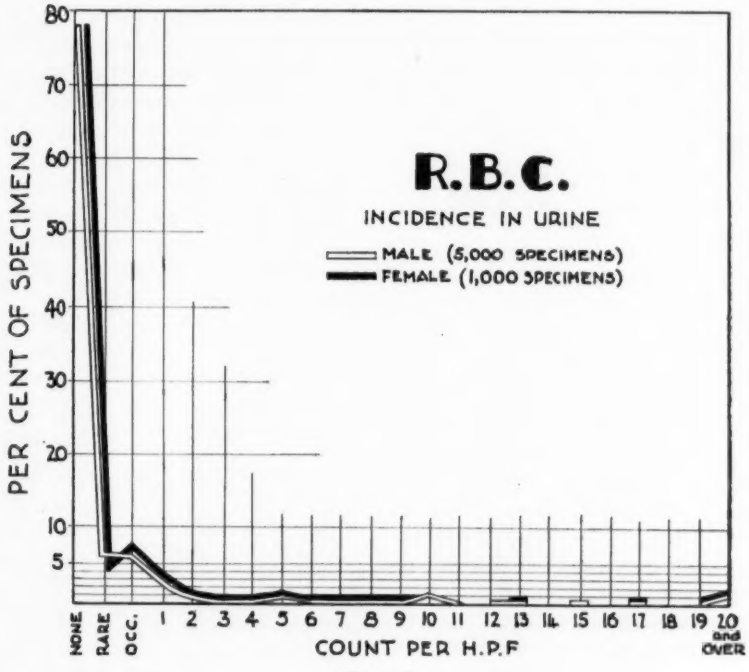

Figure 2

occur for white cells, men and women, at about 1-2 per hpf and for red cells, men and women, at occasional. The breaks, however, are not wholly complete but fade through an equivocal range of several cells per hpf, more obvious with respect to white cells in the urine of women.

Arranged in graphic form, Figures 1 and 2 show the breaks dramatically, though the small scale unduly minimizes the fade-out areas. In Figure 1, a slight rise at 5 cells per hpf has no significance; it is merely an artifact resulting from an unsuspected idiosyncracy, a habit of reporting 4-6, which averages 5. A similar artifact occurs in Figure 2.

In Figure 2, it appears that despite a significant break most specimens show no red cells at all. However, the break occurs *after* occasional cell.

Summary

In the vast majority of urine sediments the white cells do not exceed 1-2 per hpf and the red cells, occasional. Correlation with previous findings, by Addis, in apparently healthy persons is presented. A count of several cells per hpf remains of equivocal significance.

27 Beaver Pl. (8).

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The Results of Treatment for Obesity

A Review of the Literature and Report of a Series

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The current widespread concern with weight reduction rests on at least two assumptions: first, that weight-reduction programs are effective; second, that they are harmless. Recent studies indicate that such programs may be far from harmless.[1,2] This report documents their ineffectiveness. The results of treatment, as reported in the medical literature of the past 30 years, are first reviewed. The results of routine treatment of 100 consecutive obese persons in the Nutrition Clinic of the New York Hospital are then reported.

Review of the Literature

Hundreds of papers on treatment for obesity have been published in the past 30 years. Most, however, do not give figures on the outcome of treatment, and of those that do, most report them in such a way as to obscure the outcome of treatment of individual patients. Some authors, for example, report the total number of patients and the pounds lost without making clear how many patients achieved satisfactory results. Others report rates of weight loss of groups of patients for whom the duration of treatment was short or even unspecified. Still others use as their standard the percentage of excess weight lost, without noting the amount in pounds. Perhaps the greatest difficulty in interpreting the results of weight-reduction programs, however, is due to the exclusion from reports of patients who did not remain in treatment or were otherwise "uncooperative." Such patients probably represent therapeutic failures, and they certainly constitute an impressive part of any group. Reports which exclude them, therefore, are not useful in evaluating treatment. If papers with these shortcomings are omitted, the vast literature on treatment for obesity shrinks to just eight reports.[3-10] These are summarized in Table 1.*

Interpretation of these results is complicated by two omissions: the method of selecting patients and their degree of overweight. The first of these factors is often difficult to ascertain; the second makes reporting so complex as almost to obviate comparisons between groups. To facilitate such comparison we have listed the per cent of patients in each series who lost 20 and 40 lb., irrespective of their original weights. Although these criteria may introduce a bias in favor of treatment of more severely obese persons (who have more weight to lose), they have the virtue of being sufficiently modest to be widely applicable. Twenty pounds is indeed a small weight loss for the grossly overweight persons who are the subjects of these reports.

The review in Table 1 reveals two significant points. The results of treatment for obesity are remarkably similar and remarkably poor. Thus, with the exception of Feinstein, no author has reported even the modest success of a 20 lb. weight loss

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* The present study deals only with outpatient treatment of obesity. Inpatient treatment, with its far greater control over food intake, does not present the same problems.

TABLE 1.—*A Summary of Results of Treatment for Obesity as Reported in Medical Literature During the Past Thirty Years*

Author	Type of Treatment	Patients, No.	Weight Loss, % of Patients			
			Less Than 10 Lb	10-20 Lb.	More Than 20 Lb.	More Than 40 Lb.
Fellows (1931)	Employees clinic: individual instruction & self-selected diet	294	47	27	26	5
Evans (1938)	Private practice (internist): 600 Cal. diet	130	59	19	22	5
Gray & Kallenbach (1939)	Nutrition clinic: 900 Cal. diet & thyroid	314	52	20	28	8
Osserman & Dolger (1951)	Diabetes clinic: dextro amphetamine (Dexedrine)	55	35	36	29	2
Munves (1953)	Home economics research: interview or group discussion	48	61	27	12	4
Harvey & Simmons (1954)	Group psychotherapy project: 1,000 Cal diet	290	47	30	23	6
Young et al. (1955)	Experimental nutrition clinic: interview & diet	131	40	32	28	8
Feinstein et al. (1958)	Obesity research clinic: 900 Cal. formula diet	106	17	24	59	31

in more than 29% of his patients. The per cent of patients losing 40 lb. is far smaller. Furthermore, the results in six of the eight reports are within seven percentage points of each other. This remarkable uniformity, despite the widely differing circumstances of the studies, increases the assurance with which these results may be regarded.

These reports were all written by persons with a particular interest in obesity, by experts in the field. It is probable that their results, poor as they seem, are nevertheless better than those obtained by the average physician. To ascertain the results of treatment in routine clinic practice, a study was undertaken of the results of treatment for obesity of 100 consecutive obese persons in the Nutrition Clinic of the New York Hospital. These results follow.

Results in a Nutrition Clinic

One of the functions of the Nutrition Clinic of the New York Hospital is instruction of overweight persons in weight-reduction diets. Since there is no obesity clinic or other specialized weight-reduction agency in connection with the hospital, all reducing diets prescribed in every clinic are supervised in the Nutrition Clinic. The obese persons seen in this clinic thus represent a very large per cent and a relatively unbiased sample of the obese patient population of the hospital.

During a three-month period, one of us (M. M.) interviewed each obese person admitted to the Nutrition Clinic. (Obesity was considered as a body weight which exceeded by 20% the ideal weight for a person of medium build as established by the tables of the Metropolitan Life Insurance Company.[11]) Patients were referred from every clinic in the hospital, but the greatest number came from the General Medical Clinic. There was a wide variety of diagnoses in addition to obesity, but the health of most of the patients was good. Ninety-seven of the patients were women, and only three were men. Median age was 45, with a range from 20 to 67, while the median per cent of excess weight was 44, with a range from 21 to 119.

At their initial clinic visit the patients were instructed in balanced weight-reduction diets of from 800 to 1,500 Cal. They were seen thereafter at intervals of from two to six weeks in the Nutrition Clinic, and they also continued treatment for their original complaints in the clinic from which they had been referred. No drug therapy was administered in the Nutrition Clinic,

but anorexigenic drugs were prescribed for a few patients in other clinics.

Two and one-half years later the patients' charts were reviewed to determine the outcome of their efforts at weight reduction. The lowest weight reached after the first Nutrition Clinic appointment was considered the therapeutic effect, even though the weight had subsequently increased.

Results of Treatment.—The results of treatment in the Nutrition Clinic were even poorer than those reported in the literature. Only 12 of the 100 patients succeeded in losing more than 20 lb. at any time during the two years, and only one of these was able to lose more than 40 lb. Furthermore, 39 patients did not return to the Nutrition Clinic after their first visit, and, what is even more striking, 28 never returned to any clinic of the hospital. Since admission to the Nutrition Clinic occurs entirely by referral from other clinics, this represents the rupture of at least two therapeutic relationships.

Maintenance of Weight Loss.—Maintenance of weight loss is even more difficult to appraise than its achievement. Five studies indicate,[5,8,10,13,14] however, that maintenance is no more successful than initial weight loss; a majority of persons regain a majority of the pounds lost. We also found this to be the case. Our results are summarized in Table 2. In this Table any person who maintained a weight loss of 20 lb. or more is classified as a "success"; any person whose weight was within 19 lb. of the starting weight is a "failure." By these criteria, only six persons were still successful one year after treatment, and only two persons were successful two years after treatment. Four of the nine "failures" has regained all of the weight lost by the time of the two-year follow-up. Of the remaining five "failures," one had lost a maximum of 51 lb. and then had regained 35 of them; one had lost 32 lb. and regained 18 of them. Three lost 21 or 22 lb.; they regained, respectively, 13, 9, and 6 lb.

TABLE 2.—*Two-Year Follow-Up of Patients Who Lost Weight* *

	Success	Failure	No Information
End of treatment	12	--	--
1 yr. later	6	5	1
2 yr. later	2	9	1

* Study covers 12 patients, in the Nutrition Clinic of New York Hospital, who achieved a 20 lb. weight loss during treatment.

Ill Effects of Dieting.—Attention has lately been drawn to the occurrence of emotional disturbances in obese persons in the course of attempts at weight reduction.[1] Such disturbances, occurring in one-third of the obese persons treated in a psychosomatic clinic, are the subject of a more detailed report by one of us.[2] This report, by a psychiatrist, is subject to the criticism that it is based on a highly selected group of patients. The present study permitted us to ascertain more nearly the true incidence of untoward effects of attempts at weight reduction among the obese population as a whole. During the initial interview by the dietitian, each patient was questioned as to any ill effects encountered during her most recent weight-reduction regimen and attributed by her to the regimen. This aspect of the study, then, was retrospective and provided information which is not strictly comparable to that obtained in its other aspects. No diagnostic formulation of the patient's complaints was attempted, but the presence and the character of the symptoms were recorded.

Of the 100 patients referred for reducing diets, 72 reported that they had attempted dieting previously, several on more than one occasion. Of these 72 patients, 54% reported the presence of symptoms during at least one reducing regimen, and 55% of all such regimens were characterized by the presence of symptoms. The commonest complaints were "nervousness" and "weakness," each reported by 21% of the patients. Less frequent symptoms were "irritability" in 8%, "fatigue" in 5%, and "nausea" in 4%.

No attempt was made to study emotional disturbances which occurred in the course

of the treatment prescribed in the Nutrition Clinic. Such information, however, became available during the investigation of four patients who had successfully reduced and had then discontinued treatment. One was a man who achieved the greatest weight loss of the study, from 241 lb. to 190 lb. He reported that the reducing regimen had been associated with mounting tension which culminated in what was diagnosed as an acute schizophrenic reaction. He was treated with tranquilizers in a hospital for four months and was discharged much improved. He discontinued dieting shortly before hospitalization and gradually regained 35 lb. For the past two years his weight has remained stable and he has been in good health.

Evaluation of Possible Indices of Prognosis

In view of the ineffectiveness and ill effects of weight-reduction regimens, knowledge of factors influencing prognosis would be helpful. If it were possible to select in advance those patients most likely to benefit from such regimens, others could be spared suffering and fruitless effort and physicians could concentrate on those in whom their intervention might make the difference between success and failure. Furthermore, such information might provide a basis for differentiating different types of obesity and, ultimately, for understanding the causes of this disorder.

In the present study four factors were investigated for their usefulness as indices of prognosis. They were (1) sex of the patient, (2) presence of the "night-eating syndrome," (3) the outcome of previous attempts at weight reduction, and (4) response to the Taylor Test for Manifest Anxiety. Only the first of these indices, the sex of the patient, seemed of predictive value.

Sex of the Patient.—Sex of the patient has not, to our knowledge, been previously suggested as a possible factor in the success of efforts at weight reduction. We were, therefore, surprised to discover that whenever results of treatment have been reported according to the sex of the patient, men have been shown to be more successful than women. These results, together with those of the present study, are summarized in Table 3.[4,9] It will be noted that in each study a far higher percentage of men than women were able to achieve the modest success of a 20 lb. weight loss. These differences are significant at the 2% level (Feinstein), the 7% level (Munves), and the 2% level (present series), as determined by direct calculation of probability.

TABLE 3.—*Relation of Sex of Patient to Outcome of Attempts at Weight Reduction* *

	Feinstein et al.		Munves		Present Series	
	Success	Failure	Success	Failure	Success	Failure
Men	10	1	5	15	2	1
Women	50	45	1	27	10	87

* "Success" is defined here, as elsewhere in this report, as a 20 lb. weight loss.

The discrepancy between results of treatment for men and for women is even more pronounced if 40 lb. is considered as a criterion of success. Sixty-eight per cent of the men in Feinstein's report lost 40 lb., as compared with twenty-eight per cent of the women. Furthermore, the only four subjects in Munves' study to lose 40 lb., and the only one in the present study who lost this much, were all men. It is worthy of note that these differences are not a result of differences in age, per cent overweight, or pounds overweight between the men and the women.

A fourth study,[12] reported in a somewhat different manner, also found men to be more successful than women in attempts at weight reduction. The mean percentage of excess weight lost by a group of 13 men was 46%, as compared with a value of 34% for 97 women.

The Night-Eating Syndrome.—A previous report has described a peculiar pattern of food intake characterized by morning anorexia, evening hyperphagia, and insom-

nia.[15] This "night-eating syndrome," which appears to be confined to obese persons, was found in 66% of those attending a psychosomatic clinic. Attempts at weight reduction by persons manifesting the syndrome were usually unsuccessful. An attempt was made to determine if this were also true of a less carefully selected population.

The results of the present study gave no support to the expectation that the night-eating syndrome might be of value in predicting inability to lose weight. Although 12 of the 14 persons manifesting the syndrome were indeed unsuccessful, 2 succeeded in losing more than 20 lb. This rate of failure is no higher than that among persons free of the syndrome.

There are at least two possible explanations of this finding. Presence of the night-eating syndrome may, indeed, be of no relevance to the outcome of attempts at weight reduction. On the other hand, the low incidence of persons manifesting the night-eating syndrome and of those successful in losing weight makes it unlikely that any but the closest association could be demonstrated.

Outcome of Previous Attempts at Weight Reduction.—It has been suggested that previous successful weight reduction increases the probability of successful weight reduction in any later effort, and, conversely, that failures in previous attempts bode ill for further trials.[16] No support for this hypothesis was obtained.

TABLE 4.—*Relation of Outcome of Previous Attempts at Weight Reduction to Outcome of Current Attempt* *

	Previous Outcome			
Current Outcome	Success	Failure	No Attempt	Total
Success	2	8	2	12
Failure	14	32	14	60
Did not return	7	9	12	28
Total	23	49	28	100

* It will be noted that previous success or failure is not predictive of the outcome of later attempts at weight reduction.

Table 4 reveals that of the 23 persons who had reported any previous dietary success, only 2 were able to lose 20 lb. On the other hand, of the 49 who had failed in all previous attempts at weight reduction, 8 were successful in this one. The results were thus the antithesis of those predicted by the hypothesis: probability of success was actually slightly higher for persons with previous dietary failure.

Taylor Test for Manifest Anxiety.—It is widely believed that emotional disturbances contribute to the pathogenesis of obesity as well as to the failure of attempts at weight reduction. An effort was made, therefore, to determine if an index of emotional disturbance could predict the outcome of attempts at weight reduction. For this purpose the Taylor Test for Manifest Anxiety was administered to each patient during the initial visit to the Nutrition Clinic. This test is a 50-item true-false questionnaire comprising those items of the Minnesota Multiphasic Personality Inventory which deal with manifest, or free, anxiety.[17] One point is scored for each response indicating the presence of anxiety; the higher the score, the greater the anxiety. We postulated that subjects with higher scores should have a poorer prognosis for weight reduction. A corollary hypothesis, deriving from the purported relationship of emotional disturbances and obesity, was that obese persons should show higher scores than normal controls.

Only the corollary hypothesis was validated. The mean score of the 100 obese persons was 18.0±9.5. This contrasts with scores of 15.3±7.9 and 15.9±7.5 for two control groups of 750 and 414 subjects respectively,[18] a difference significant at the 1% level. These obese persons appear to show greater anxiety than normal, as anxiety is measured by the Taylor test. The test was not, however, predictive of the outcome of attempts at weight reduction. The subjects who reduced successfully actually had higher anxiety scores than those who failed, although the difference did not approach statistical significance.

Comment

In recent years the ill effects ascribed to excessive body weight have received wide attention, as have the benefits to be achieved by weight reduction. As a result many physicians and their patients, who had formerly looked upon weight reduction as a cosmetic conceit, have come to consider it a therapeutic imperative. A variety of lay institutions, notably the magazines for women, has seized upon this growing interest in weight reduction and has helped to magnify it to the proportions of a national neurosis. The influences responsible for this unfortunate development are not fully understood. The medical profession, however, must accept some responsibility. For underlying the extravagances of the miracle diets and the reducing salons are certain widely held medical attitudes.

Many years ago detailed metabolic studies demonstrated that human beings do not defy the second law of thermodynamics and that excessive body fat results from an excess of caloric intake over caloric expenditure. This not unreasonable finding was thereupon enshrined as the dictum that "all obesity comes from overeating," and the treatment of obesity lost its glamour. The physician's job, it seemed, was simply to explain that semistarvation reduces fat stores, to prescribe a diet for this purpose, and to sit by. If the patient lost weight as predicted, this merely confirmed the comfortable feeling that treatment of obesity was really a pretty simple matter. However, if, as so often happened, the patient failed to lose weight, he was dismissed as uncooperative or chastized as gluttonous. It was the rare physician who entertained the possibility that failure to follow a regimen might in itself be a medical problem. Rarely have physicians so readily surrendered a part of their domain to moralizing, indifference, and despair.

What have been the consequences of this surrender? First, the naive optimism of the medical profession about treatment for obesity has been widely accepted by the lay public. Most obese persons feel that they should be able to lose large amounts of weight in a short time and with little discomfort. When they find that these expectations are not realized and when they encounter the irritation of their physicians over this failure, they turn to any agency which promises results. The profusion of nonmedical agencies testifies to the extent of our patients' needs and to the magnitude of our failings.

How may the medical profession regain its proper role in the treatment of obesity? We can begin by looking at the situation as it exists and not as we would like it to be. We can acknowledge that treatment for obesity is a terribly difficult business, one in which our experts achieve only modest success, and the rest of us, even less. It is a treatment which can be fraught with danger, a treatment not to be undertaken lightly by any obese person and by some perhaps not at all. Certainly weight reduction is not a matter to be left to unqualified practitioners.

Lowering our level of aspiration may go far toward achieving our aims. If we do not expect weight reduction as a matter of course we may be able to accord due recognition to success. If we do not feel obliged to excuse our failures we may be able to investigate them. Learning to respect the complexities of their illnesses will help us to respect our patients. And the patient who has the respect of his physician has little reason to seek elsewhere for treatment.

Summary

A review of the literature on outpatient treatment for obesity reveals that the ambiguity of reported results has obscured the relative ineffectiveness of such treatment. When the per cent of patients losing 20 and 40 lb. is used as a criterion of success, the reports of the last 30 years show remarkably similar results. Although the subjects of these reports are grossly overweight persons, only 25% were able to lose as much as 20 lb. and only 5% lost 40 lb.

Routine treatment of 100 consecutive obese outpatients in the Nutrition Clinic of a large teaching hospital was even less successful. Only 12% were able to lose 20 lb., and only 1 patient lost 40 lb. Furthermore, 28% of the patients never returned to either the Nutrition Clinic or the referring clinic after their first visit. Two years after the end of treatment only two patients had maintained their weight loss.

A search for criteria which might aid in predicting the outcome of attempts at weight reduction revealed only one: Men appear to be more successful than women.

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Studies of Proteolytic Enzymes in Cerebrospinal Fluid

Capacity of Incubated Mixtures of Cerebrospinal Fluid and Plasma Proteins to Form Vasodilator Substances That Contract the Isolated Rat Uterus

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A study of tissue fluid removed from regions of local tenderness in the scalp during vascular headache of the migraine type indicated that this fluid contained a pain-threshold-lowering substance.[4,15] It had many of the properties of vasodilator polypeptides derived from plasma proteins. Armstrong et al.[2,3] demonstrated that such polypeptides were present in blister fluid, in fluid collected from painful joints, and in inflammatory pleural fluid. At about the same time, Hilton and Lewis [11] described a proteolytic enzyme present in saliva and in saline perfusate of the salivary gland. This enzyme formed vasodilator polypeptides when incubated with plasma proteins. Increased amounts of enzyme were observed during heightened metabolic activity of the gland. Hilton and Lewis concluded that the enzyme and polypeptide are responsible for local vasomotor control in the salivary gland. The properties of the polypeptide correspond closely to those of "bradykinin," the name given by Rocha e Silva, Beraldo, and Rosenfeld [16] to the substance or substances produced on incubation of snake venom or trypsin with serum, plasma, or plasma globulins.

When the incubated mixture was applied to smooth muscle (isolated rat uterus or guinea pig ileum) contractions occurred that were delayed, slow, and sustained. Bradykinin probably is identical with "kallidin," the name given by Frey, Kraut, and Werle [9] to a polypeptide produced by the action of tissue extracts on plasma protein. The active agent in the tissue juices is a proteolytic enzyme and has been called "kallikrein." Plasmin can form such polypeptides.[15a]

Proteolytic enzymes that form vasodilator polypeptides of the bradykinin type are known to be present in glandular secretions other than saliva—for example, in pancreatic juice [19,20] and in human forearm sweat.[7,8] They have been found in urine.[9] Also, the subcutaneous tissue of the forearm contains a vasodilator polypeptide of this type when the subject is placed in an environment warm enough to induce widespread vasodilatation in the skin and sweating.[7,8,8a] Its presence probably is related to the vasodilatation that occurs in the skin of the forearm when body temperature is raised by immersing the feet and legs in hot water at 40 C. The initial phase of such vasodilatation is linked with itching and lowered pain threshold.[10] The demonstration by Hilton and Lewis [11] that a protease-polypeptide system is implicated in functional vasodilatation of the salivary gland suggests that if protease and polypeptide be present in other tissues such a system may take part in vasomotor control there as in the salivary glands.

Calf brain was shown by Kies and Schwimmer [13] to contain a proteolytic enzyme. However, its proteolytic activity could not be observed when the pH was in the usual physiological range. Ansell and Richter [1] reported on intracellular neutral

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proteinase in brain tissue which breaks down brain protein at pH 7.4. The reaction could be detected only in fresh brain tissue examined shortly after death. They concluded that this intracellular enzyme was concerned in the continuous breakdown and resynthesis of tissue proteins. Ungar et al.[17] demonstrated an increased protease content in rat brain following brief electrical stimulation of the sciatic nerve and showed that protein denaturation and breakdown, in addition to increased protease content, occurred following sustained stimulation (i. e., for 20 minutes). They also observed increased protease activity and protein denaturation following induced convulsions.

It has been postulated in this laboratory [4] that vascular headache of the migraine type is an epiphenomenon arising as a sequel of the excessive operation of the normal mechanism for functional vasodilatation in the head. The painful dilatation, chiefly of some of the branches of the external carotid artery, is viewed as incidental to dilatation of the branches of the internal carotid artery (usually nonpainful), perhaps because of the common innervation of these vessels. Since the fluid in the tissues surrounding the branches of the external carotid artery contained vasodilator polypeptides of the bradykinin type,[15] the possibility that a vasodilator polypeptide system (protease and polypeptide) also was implicated in functional vasodilatation within the central nervous system seemed worthy of exploration. Furthermore, it seemed pertinent to ask whether excessive amounts of these substances were present in pathological states within the central nervous system.

Attempts have been made to ascertain whether and under what circumstances such an enzyme and vasodilator system is present in the central nervous system. To this end cerebrospinal fluid was collected from subjects with (1) active disease of the central nervous system; (2) inactive, nonprogressive, or no disease of the central nervous system; (3) vascular headache of the migraine type; (4) sustained nervous stimulation and pain arising from disorders of the legs or pelvic organs, and (5) disease syndromes classified as chronic schizophrenia. Specimens were either assayed at once or immediately frozen in solid carbon dioxide.

Method for Assaying Protease and Vasodilator Polypeptides with a Smooth Muscle Preparation

1. A strip of uterus removed from an anestrous rat was suspended in a 12 cc. chamber containing 10 cc. of de Jalon's modification of Ringer's solution at 29 C. One end of the strip was connected by a cotton thread to a lever that recorded contractions on a kymograph.

2. The sensitivity of the preparation was assessed by the response of the uterus to a polypeptide ("bradykinin") standard prepared by (*a*) incubation of trypsin and bovine globulin for 20 minutes at 37 C, (*b*) precipitation of protein by hot alcohol and, (*c*) lyophilization and subsequent redilution with distilled water of the soluble breakdown products contained in the supernatant liquid. (If the response to 0.2 cc. of this polypeptide standard was inadequate, the muscle preparation was discarded.)

3. Freshly collected or thawed C. S. F. (0.2 cc.) was added to the chamber. If contractions were observed the specimen was recorded as inducing a type I reaction. If no contractions were observed, 0.2 cc. of the specimen was incubated with 0.2 cc. of an 8% solution of bovine globulin (fraction II) for 3 minutes at 29 C. If the resultant mixture induced contractions, the specimen was recorded as inducing a type II reaction. If no contractions were observed, the specimen was recorded as negative.

It was inferred that the specimens which gave type II reactions contained detectable amounts of a proteolytic enzyme capable of acting on plasma

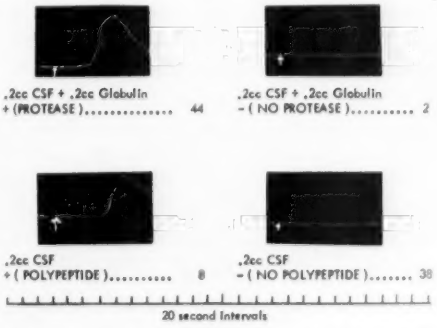
.2cc CSF + .2cc Globulin
+ (PROTEASE)..... 44
.2cc CSF + .2cc Globulin
- (NO PROTEASE)..... 2
.2cc CSF
+ (POLYPEPTIDE)..... 8
.2cc CSF
- (NO POLYPEPTIDE)..... 38
20 second Intervals

Fig. 1.—Rat uterus bioassay of cerebrospinal fluid collected from 46 subjects with active disease of the central nervous system.

TABLE 1.—*Forty-Six Subjects with Active or Progressive Disease of the Central Nervous System*

Subjects, No.	Disease Category	C. S. F. Total Protein, Mg. % Range	Mean	Type II	Type I	Negative
13	Cerebrovascular accidents (recent)	6 (32–63)	44	6	0	0
		5 (108–158)	140	3	2	0
		2 (with gross blood)	1454	0	2	0
8	Neoplasms of central nervous system	6 (25–193)	90	5	1	0
		1 (with gross blood)	980	1	1	1
		1	62	0	0	0
7	Cerebral atrophy or degeneration (some with arteriosclerosis)	6 (27–45)	40	4	2	0
		1	153	1	0	0
4	Radiculitis (cervical & lumbar)	3 (44–76)	56	3	0	0
		1	39	0	0	1
4	Multiple sclerosis	30–55	41	4	0	0
2	Collagen syndromes	29 & 60	45	2	0	0
2	Diabetic neuropathy	129 & 148	138	2	0	0
1	Encephalitis		30	1	0	0
1	Seizure disorder (frequent & severe)		49	1	0	0
1	Polyneuropathy (ideopathic)		108	1	0	0
1	Huntington's chorea		46	1	0	0
1	Brain trauma (acute)		39	1	0	0
1	Adhesive arachnoiditis (subacute)		257	1	0	0
—		—		—	—	—
46		46 specimens		36	8	2

proteins (globulin) to form polypeptides of the bradykinin type and that specimens which gave type I reactions contained detectable amounts not only of the enzyme but of the products of proteolytic activity as well presumably polypeptides.

Results

Subjects with Active Disease of Central Nervous System.—Cerebrospinal fluid specimens from 46 subjects with active disease of the central nervous system were assayed (Table 1). Characteristic contractions were induced by 44 of the 46 incubated globulin-cerebrospinal fluid mixtures, including those with total cerebrospinal fluid protein content within the normal range.* Moreover, of these 44 specimens, 8 induced contractions when the cerebrospinal fluid alone was added to the rat uterus chamber.

Type I reactions occurred most frequently in subjects with greatly elevated total protein content (six of eight reactions were induced by specimens in which total protein was 90 mg. % or above). However, two such reactions were induced by two specimens with total protein content within the normal range. Also, eight specimens with a total protein content above 90 mg. % resulted in type II but not type I reactions. reactions.

Subjects with Inactive, Nonprogressive, or No Disease of Central Nervous System.

Cerebrospinal fluid specimens from subjects with inactive, nonprogressive, or no disease of the nervous system (Table 2) only rarely induced contractions of the rat uterus under the conditions of the assay (2 of 41 specimens studied).

Comment: It was inferred that the cerebrospinal fluid of subjects with active

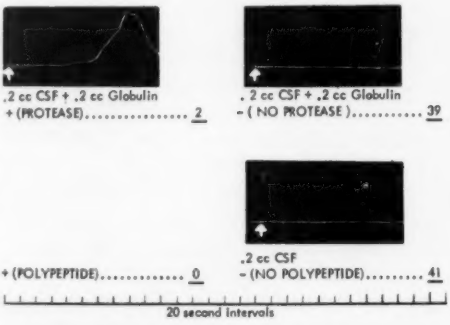
.2 cc CSF + .2 cc Globulin
+ (PROTEASE)..... 2
. 2 cc CSF + .2 cc Globulin
- (NO PROTEASE)..... 39
.2 cc CSF
+ (POLYPEPTIDE)..... 0
- (NO POLYPEPTIDE)..... 41
20 second Intervals

Fig. 2.—Rat uterus bioassay of cerebrospinal fluid collected from 41 subjects with inactive, nonprogressive, or no disease of the central nervous system.

* The low content of protein in the cerebrospinal fluid probably accounts for the observation that the protease could be demonstrated in the absence of observable amounts of the polypeptide.

TABLE 2.—*Forty-One Subjects with Inactive, Nonprogressive, or No Disease of the Central Nervous System*

Subjects, No.	Disease Category	C. S. F Total Protein, Mg. % Range	Mean	Type II	Type I	Negative
10	Cerebrovascular accident (old, small or vascular insuf.)	20-42	34	0	0	10
4	Myasthenia gravis	28-64	40	0	0	4
4	Seizure disorder (idio., not freq. or recent)	24-41	33	0	0	4
3	Progressive muscular dystrophy	19-38	38	0	0	3
2	Pituitary adenoma	20 & 37	29	0	0	2
2	Primary lateral sclerosis (old)	39 & 45	42	0	0	2
2	Bell's palsy	20 & 40	30	0	0	2
2	Myelopathy (old, post. sp. anaes., idio.)	48 & 56	52	0	0	2
2	Cerebral dysplasia	16 & 24	20	0	0	2
2	Occl. vasc. dis. (periph. neuropathy)	36 & 45	40	0	0	2
6	Syringomyelia, old polio. and misc.	32-46	39	0	0	6
1	Dietary insuf. (senile osteoporosis)		32	1	0	0
1	Hypert. vas. dis. (cerv. osteoarthritis)		40	1	0	0
41		41 specimens		2	0	36

disease of the central nervous system contained larger amounts of the protease than did fluid collected from subjects without such disease.

Subjects with Vascular Headache of Migraine Type.—Eighteen specimens of cerebrospinal fluid were collected from subjects (Table 3) during or one day after vascular headache of the migraine type. Type II reactions were observed in 15 of these specimens. Type I reactions were induced by three. All of the latter were collected from subjects with involvement of both intracranial and extracranial tissues. Eight specimens were collected in the headache-free interval (more than seven days after a migraine attack). Seven of these resulted in negative reactions. One specimen, collected eight days after the cessation of pain but during a continued but transient oculomotor palsy (ophthalmoplegic migraine), gave a Type I reaction.

Comment: These observations indicated that increased protease concentration in the C. S. F. occurs during vascular headache of the migraine type. Further, a smooth-muscle-contracting substance is present in the C. S. F. in subjects with such headache in which intracranial as well as extracranial tissues are implicated. Since vasodilatation of the intracranial vessels is associated with vascular headache of the migraine type,[21] the demonstration of protease and polypeptide in the C. S. F. supports the hypothesis that the protease-polypeptide system is implicated in local vasomotor control of the

TABLE 3.—*Nineteen Subjects with Vascular Headache of the Migraine Type*

Observations	C. S. F. Total Protein, Mg. % Range	Mean	Type II	Type I	Negative
In subjects with pain mainly from extracranial tissue					
14 during headache	22-60	36	13	0	1
2 one day after headache	24 & 78		2	0	0
7 one week after headache	22-49	37	0	0	7
In subjects with pain also from intracranial tissue					
2 * during headache	23 & 41		0	2	0
1 † 8 days after headache	88		0	1	0
26 observations			15		8

* One had transient hemiplegia and aphasia.
† Ophthalmoplegic migraine.

intracranial vessels. The intracranial vasodilatation during a migraine attack, however, rarely is painful; the pain stems chiefly from the branches of the external carotid artery. In those instances in which there is pain from noxious stimulation of intracranial vessels, it is inferred that a pain threshold lowering substance is present in relatively high concentrations in pain-sensitive regions within the cranium, particularly about the vessels at the base of the brain.

Subjects with Disorders of Legs or Pelvic Organs (Sustained Noxious Stimulation and Pain in Twelve Subjects).—In order to examine the effect of sustained noxious stimulation and pain on the protease-polypeptide system in the cerebrospinal fluid, specimens of fluid were collected from 25 subjects with disorders of the legs or pelvic organs immediately preceding surgical procedures. Thirteen subjects had experienced little or no pain during the 72 hours preceding collection. Of these, 2 specimens resulted in type I reactions and 11 resulted in negative reactions. On the other hand, 12 subjects had experienced moderately severe or severe sustained pain during the 72 hours preceding the collection of C. S. F. Of these, type II reactions were observed with 9 specimens. Two gave type I reactions. One specimen gave a negative reaction (Table 4).

Comment: It was concluded that sustained noxious stimulation and pain were associated with increased protease content in the cerebrospinal fluid. This observation suggests that increased proteolytic activity in the extracellular fluid of the central nervous system occurs not only during active degeneration and frank inflammation but also during states of sustained excitation within the central nervous system.

TABLE 4.—*Twenty-Five Subjects with Diseases of the Legs or Pelvic Organs*

Pain & Reactions During Previous 72 Hr.	Subjects, No.	C. S. F. Collected Immediately Preceding General Surgical Procedures		
		Type II	Type I	Negative
No or mild pain, relatively relaxed & calm	13	2	0	11
Probable pain but no precise data	3	1	1	1
Sustained pain, restless, frightened, & disturbed	9	8	1	0

Subjects with Disorders Classified as Chronic Schizophrenia.—In Table 5 the observations made on the cerebrospinal fluid of 41 hospitalized patients with schizophrenic reactions are shown. Their ages were between 20 and 50 years. All were male, and none had evidence of other significant disease. None was greatly overactive or assaultive at the time of study. Some had hallucinations, and most had delusions. Remission in a few was partial but insufficient to warrant discharge. All were ambulatory, and none exhibited evidence of dietary insufficiency. One subject had occasional convulsive seizures that first occurred after he had had many electrically induced convulsions in the past. The frequency of these seizures was much reduced by medication. No subject had had electrically induced convulsions in the year previous to study. Type II reactions were observed with specimens from 35 subjects. Four gave type I reactions. Two gave negative reactions.

TABLE 5.—*Forty-One Subjects with Disease Classified as Chronic Schizophrenia*

	No.	Total Protein
Type II	35	23-73, average 40 mg. %
Type I	4	25, 27, 35, 42 mg. %
Negative	2	39, 48 mg. %
	41	

Consideration of the daily medication received is pertinent, since Ungar et al.[18] demonstrated that in experimental animals the administration of reserpine led to increased protease content in the resting brain, whereas chlorpromazine inhibited the increase in protease observed after electrical stimulation. The medication received by these subjects is shown in Table 6. It is

TABLE 6.—*Pharmaceutical Agents Administered to Forty-One Patients with Disease Classified as Chronic Schizophrenia*

Patients, No.		Type II	Type I	Negative
9	Phenothiazine derivatives *	7	0	2
10	Reserpine †	18	2	0
20	None ‡	18	2	0
1	Diphenylhydantoin	1	0	0
1	Phenobarbital	1	0	0

* 3 received amobarbital sodium (Amytal) (195 mg.) shortly before the lumbar tap.

† 3 received amobarbital sodium (Amytal) (195 mg.) shortly before the lumbar tap.

‡ 2 received amobarbital sodium (Amytal) (195 mg.) and 1 received meprobamate (400 mg.) shortly before the lumbar tap.

TABLE 7.—*Properties of an Agent Resulting from Incubation of Active C. S. F. with Globulin*

1. Induces pain when applied to exposed blister base
2. Increases capillary permeability
3. Is a vasodilator and lowers blood pressure when injected into the venous circulation
4. Contracts isolated rat uterus, guinea pig ileum, and fundus of rat stomach
5. These contractions not inhibited by atropine, antihistaminics, or dihydroergotamine in amounts large enough to inhibit contractions induced by acetycholine, histamine, or serotonin, respectively
6. Contractions inhibited by salicylate and by soluble adrenal steroids

evident that the use of these agents is not responsible for the increased protease observed.

Comment: It has been shown previously in this laboratory [5,6] that subjects with disease classified as schizophrenia exhibit a fall-off in highest integrative functions, in many ways resembling that observed in subjects with serious brain damage. Impairment of highest-level brain functions also was observed in subjects with prolonged adaptive difficulties and severe anxiety. These latter subjects, as well as many of those with schizophrenia, were referred to as being in the "unadapted state," a term employed to refer to the totality of reactions (physiological, behavioral, and attitudinal) present in subjects who for long periods have perceived themselves as severely or overwhelmingly threatened and have been unable to achieve adequate overall adaptation. Prolonged disturbance in the modulation of excitation and inhibition within the central nervous system is inferred to be an aspect of the unadapted state.

Therefore, it is of special interest that the cerebrospinal fluid of patients with schizophrenia contains an abnormal amount of protease, as also was found in those with active inflammatory and degenerative disease or prolonged excitation of the central nervous system. This observation suggests that a significant (yet perhaps reversible) alteration in metabolism occurs in the brain of patients with schizophrenia. The significance of the abnormal proteolytic enzyme activity in the disease process remains to be ascertained. The available evidence does not allow inferences as to whether the increased protease found in the cerebrospinal fluid of patients with chronic schizophrenia is a manifestation of deranged metabolic function or is a causative factory in such derangement. However, whether primary or secondary, this accumulation could contribute to impairment of the functions of the brain.†

Properties of the Substance Formed by Active Cerebrospinal Fluid (Table 7).—In order to prepare the substance for a study of its properties, specimens of cerebrospinal fluid which demonstrated a type II reaction with the rat uterus were incubated with an equal volume of an 8% solution of bovine globulin (Fraction 2) ‡ for three minutes at 37 C, and used immediately.

† It also is of interest that Krivoy [14] observed that the response of smooth muscle to Substance P (a smooth-muscle-contracting polypeptide with many of the observed properties of the polypeptide formed by active cerebrospinal fluid) is potentiated by lysergic acid diethylamide, an agent known to produce severe disturbances of brain function when administered in small amounts. Substance P can be destroyed by an enzyme present in whole brain extract. Lysergic acid diethylamide also inhibits the disappearance of Substance P when incubated with whole-brain extract.

‡ Fraction 2, while containing principally γ-globulin, also contains significant amounts of α_2- and β-components, as well as other components. The amount of protein used in these experiments is in excess; much smaller amounts of protein resulted in no diminution in the rat uterus response to incubated mixtures containing standard amounts of active cerebrospinal fluid.

The capacity of this substance to evoke pain was investigated by dropping 0.2 cc. of the incubated mixture described above on an exposed blister base on the forearm. After a delay of approximately 2 seconds, a burning pain was reported, which persisted for 10-15 seconds. Cerebrospinal fluid that demonstrated a "negative" reaction on the rat uterus did not result in pain either alone or after incubation with globulin. Globulin alone did not evoke pain. The blister base was washed with isotonic saline and at least three minutes was allowed to elapse between observations.

It has been shown [12] that polypeptides of the bradykinin type increase capillary permeability. An incubated mixture (0.1 cc.) of globulin and cerebrospinal fluid collected from a subject with a neoplasm of the central nervous system was injected intradermally into a guinea pig in an area from which all hair previously had been removed. One cubic centimeter of a 5% solution of Evan's blue dye also had been injected previously into the venous circulation. The dye spread diffusely into the region of the intradermal injection of the incubated mixture, indicating that it increased capillary permeability.

The capacity of the substance to induce vasodilatation was studied by application to the bulbar conjunctiva of a guinea pig and by observation of its action on the blood pressure of a cat when injected into the venous circulation. Application of 0.1 cc. of an incubated mixture of active cerebrospinal fluid and globulin to the bulbar conjunctiva was followed after a latency of 5-7 seconds by a gross increase in the diameter of the conjunctival vessels. Intravenous injection of 1.5 cc. of a mixture of globulin and active cerebrospinal (fluid collected during vascular headache of the migraine type) resulted in a reduction of systolic blood pressure in a cat from 160 to 140 mm. of mercury. The pressure returned to its previous level after one minute. Globulin (2 cc.), or a mixture of globulin and cerebrospinal fluid collected from another subject during a headache-free interval (which gave a negative reaction with the rat uterus), did not change the blood pressure. It was inferred that the substance is a vasodilator.

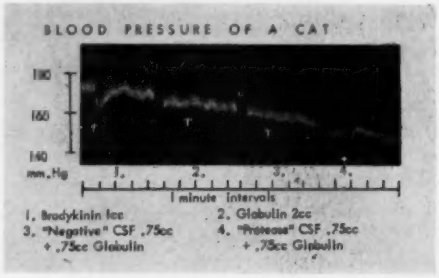

Fig. 3.—Changes in the blood pressure of a cat following intravenous injection of bradykinin, 8% bovine globulin (fraction II), and incubated mixtures of cerebrospinal fluid and globulin.

Atropine and dihydroergotamine were ineffective in blocking the contractions induced by incubated mixtures of cerebrospinal fluid and globulin when these agents were added in amounts that were effective in blocking contractions of similar amplitude induced by acetylcholine or serotonin, respectively. The active agent is not histamine, since histamine does not induce contractions of the rat uterus. However, histamine does induce contractions of the guinea pig ileum. Contractions of this muscle induced by active cerebrospinal fluid globulin mixture were not blocked by amounts of antihistaminic agent tripelennamine sufficient to block histamine-induced contractions of similar amplitude. Preliminary studies indicate that the action of the cerebrospinal fluid globulin mixture is inhibited, at least partially, (*a*) by larger amounts of dihydroergotamine than used above, (*b*) by salicylates in amounts that do not change the response to acetylcholine, (*c*) by soluble adrenal steroids, (*d*) by lysergic acid diethylamide, (*e*) by its bromine-substituted derivative (BOL), and (*f*) by chlorpromazine. Also, a stable dry powder was prepared by 10-minute incubation of active cerebrospinal fluid with globulin, precipitation with 2 vol. of boiling ethyl alcohol, centrifugation, and

lyophilization of the supernatant liquid. When rediluted, this material retained its capacity to induce contractions of the rat uterus.

Comment: These properties of incubated mixtures of active C. S. F. and globulin indicate that polypeptides of the bradykinin type are formed during such incubation. However, the rat uterus contractions observed in a Type II reaction probably represent the summated effects of several substances, some of which (for example, serotonin) may be present in cerebrospinal fluid in subthreshold amounts before incubation with globulin. Indeed, while the properties of the specimens that induced Type I reactions have been studied in only a few observations, BOL was seen to block the induced contractions in amounts similar to those required for blocking serotonin, suggesting that serotonin is the principal active agent in at least some specimens giving a Type I reaction.

Subthreshold amounts of smooth-muscle-contracting agents present in the "globulin" substrate also could contribute to the contractions observed in a Type II reaction. Further, the possibility remains that, in addition to forming polypeptides, the protease observed may liberate other smooth-muscle-contracting agents bound to protein in the "globulin" solution.

Studies of the characteristics of the protease are being made. Prior incubation of cerebrospinal fluid with streptokinase, a substance known to activate plasminogen to plasmin, neither augments Type II reactions nor results in the conversion of negative specimens to ones giving Type II reactions. These observations argue against the possibility that the protease observed in cerebrospinal fluid stems from the activation of plasminogen. The observations of Ansell and Richter [1] demonstrate that a neutral protease is present in the cells of the central nervous system. The release of intracellular protease during states of altered metabolism may account for the presence of the enzyme in cerebrospinal fluid.

Chemical Studies.—Studies of proteolytic activity in cerebrospinal fluid by chemical methods are in progress. Incubation of cerebrospinal fluid with whole human serum reveals that specimens giving "protease" reactions with the rat uterus bioassay result in the destruction of several closely related protein bands in the α-β region when examined by the method of starch-gel electrophoresis. "Negative" cerebrospinal fluid does not change the serum pattern.[22] Quantitative estimation of esterase activity by measurement of pH changes following incubation of cerebrospinal fluid with a synthetic substrate (benzoyl arginine ethyl ester) demonstrate that active cerebrospinal fluid can attack the arginine linkage.

Comment

A provisional formulation of the findings described above has been made. During periods of increased or faulty metabolism in the central nervous system the augmented catabolism results in the accumulation of protease (and possibly protein and protein breakdown products) in the extracellular and cerebrospinal fluid. Through proteolysis either within or outside minute vessels, this protease forms vasodilator polypeptides that act with other mediators to enhance local blood flow. When appropriate in amount, this response to increased catabolic products serves to meet increased tissue needs by enhancing nutrient supply. When, for whatever reason, the accumulation of extracellular protease is excessive or there is excessive formation of vasodilator polypeptides, the enhanced capillary permeability, and damage to tissue could interfere with the functional capacity of the central nervous system and may end in a sterile inflammation.

It is suggested that the protease-polypeptide system is implicated in local vasomotor control within the central nervous system and, when in excess, the components of the system may be relevant to disease.

Summary

In subjects with active disease of the central nervous system there is present a sub-

stance which, when incubated with plasma proteins, causes smooth muscle to contract. The substance could not be demonstrated with the method employed in subjects with inactive, nonprogressive, or no disease of the central nervous system except under special circumstances. It was observed in those experiencing sustained pain. It was present in subjects with vascular headache of the migraine type during and for several days after migraine attacks but not during headache-free intervals. It was present in adult patients with chronic schizophrenia. The properties of this substance suggested it to be a protease. In some subjects in whom to be a protease. The properties of the substance formed from the incubation of active cerebrospinal fluid with globulin indicated it to be a vasodilator polypeptide. In some subjects cerebrospinal fluid alone (without incubation with globulin) contracted isolated smooth muscle.

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Case Reports

Thymoma and Hemopoietic Insufficiency

EDWIN R. FISHER, M.D., and F. D. BEYER JR., M.D., Pittsburgh

The association of thymic neoplasms with myasthenia gravis is well recognized. A thymoma has been encountered in approximately one-fourth of the patients with this disorder, and a large number exhibit microscopic evidence of hyperplasia of this structure.[1] More than 50% of thymic neoplasms have occurred in persons with myasthenia gravis.[2] The exact relationship of this association is baffling. Resection of a thymoma in patients with this disorder has resulted in the alleviation of its clinical manifestations in some but not all instances, and examples of myasthenia gravis developing after the removal of such a tumor have accumulated in the literature.[3] One of the cases reported by Fisher, Coburn, and Effler[4] was unique in that the development of a thymoma provided relief from the symptoms of myasthenia gravis which had been present for 13 years.

In recent years attention has been directed to the occurrence of thymic tumors in several other clinical disorders, notably, hypoplastic anemia, agammaglobulinemia, and Cushing's disease. Their association has been considered more than fortuitous, despite the paucity of recorded examples and the failure to elucidate the mechanisms concerned with these relationships.

The purpose of this report is to describe the clinical and pathological features of an instance in which a thymic neoplasm was associated with severe hypoplasia of the bone marrow and pancytopenia. Only 16 examples of thymoma associated with hematopoietic insufficiency have been recorded previously[5-20] (Table). Approximately one-half of these have appeared in the foreign literature, and many are incompletely documented.

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From the Departments of Pathology, University of Pittsburgh and Veterans' Administration Hospital.

Report of Case

A 68-year-old white man of Greek extraction was admitted to the hospital four months prior to death because of anorexia, the loss of 20 lb. in weight, and weakness which had been present for the preceding six months. Precordial pain and exertional dyspnea were first noted two weeks prior to admission. A hydrocelectomy had been performed seven years prior to the onset of his illness. All laboratory tests, including a complete blood cell count and x-rays of the chest, were considered normal at that time. There was no history of drug administration. However, he had received a total of 785 r to the face, 560 r to the scalp, 525 r to the chest, and 150 r to the pubic area over a four-year period for seborrheic dermatitis. The radiation was unfiltered at 100 kvp.

Physical examination revealed a well-developed pallid man. His blood pressure was 162/80 mm. Hg. The pulse was 80 per minute and regular. The tongue was smooth. The liver edge was palpable 3 fingerbreadths beneath the right costochondral margin. It was smooth and nontender. Numerous petechiae were present in the skin of the extremities and face.

Laboratory studies revealed his hemoglobin to range from 3.5 gm. to 12 gm/100 ml., with the majority of determinations below 9 gm/100 ml. The higher values were noted only following transfusion. The hematocrit varied from 8.5% to 38%, and his white blood cell count, from 750 to 3800 per cubic millimeter, with the majority of counts below 2500. Differential counts revealed a neutropenia and relative lymphocytosis. Reticulocyte counts were 0.1% and 0.2% on two occasions but 0% on nine other determinations. Platelets ranged from 30,000 to 88,000 per cubic millimeter. The erythrocytes were normochromic and normocytic. Their fragility was normal. Coagulation times were normal, but bleeding times (Lee-White) were

Author	Age	Sex	Peripheral Blood	Bone Marrow	Thymic Tumor	Other Disease	Treatment	Follow-Up
1. Matras & Priesel (1928)	63	F	Pernicious anemia	*	Spindle, perithelial		*	Died; hemosiderosis
2. Radojevic & Hahn (1935)	20	M	Pancytopenia	Hypoplasia, complete	"Cystic fibrous tumor, postirradiation"		Irradiation	Died
3. Opsahl (1939)	56	M	Pancytopenia	Hypoplasia, complete	"Thymic carcinoma" invasion, left lung		*	Died
4. Davidsohn (1941)	58	F	Refractory anemia	Erythrocytic hypoplasia	"Lymphoepithelioma?" spindle cells described ‡		Many transfusions	Died; hemochromatosis?
5. Humphreys & Southworth (1945)	58	F	Refractory anemia	"Mild hypoplasia, no abnormal cells"	Spindle cell		Irradiation of tumor followed by resection	Marked improvement died 1 yr. later hemochromotosis
6. Wintrobe (1951)	16	F	Pancytopenia	Hypoplasia	Lymphocytic hyperplasia *	Myasthenia	*	Died
7. Chediak et al. (1953)	47	M	Refractory anemia	Erythrocytic aplasia	"Thymoma"		Resection	Improved
8. Pope & Osgood (1953) Ross et al. (1954)	45 (E.	F T.)	Refractory anemia	Erythrocytic hypoplasia	Spindle cell		Resection	No improvement for 4 yr.; slight improvement since
9. Pope & Osgood (1953) Ross et al. (1954) Lambie et al. (1957) Soutter et al. (1957)	45 (L.	F L.)	Pancytopenia	Erythrocytic hypoplasia	Spindle cell	Agammaglobulinemia	HN_2, splenectomy, resection	Died; hemosiderosis
10. Bakker (1954)	62	F	Refractory anemia	*	Spindle cell	Myasthenia (?)†	Resection	Reticulocyte response postop.; died 3 wk. later of myocarditis
11. Chalmers & Boheimer (1954)	48	M	Refractory anemia	Erythrocytic hypoplasia	"Lymphoepithelioma"‡	Myasthenia	Resection, splenectomy, corticotropin	Improved only after corticotropin
12. Chalmers & Boheimer (1954)	62	F	Refractory anemia	Erythrocytic hypoplasia	"Lymphoepithelioma"‡		Resection, splenectomy, corticotropin	Improved only after corticotropin
13. Weinbaum & Thompson (1955)	76	F	Refractory anemia	Erythrocytic hypoplasia	Lymphoepithelioma	Myasthenia	Transfusions	Died; hemosiderosis
14. Ramos (1956)	77	F	Severe anemia & neutropenia	Erythrocytic hypoplasia; granulocytic hyperplasia	Spindle cell	Agammaglobulinemia	Resection	Died 20 hr. postop.
15. Bayrd & Bernatz (1957)	68	F	Refractory anemia	Erythrocytic hypoplasia	"Small cell type"‡		Resection	No improvement
16. Bayrd & Bernatz (1957)	58	F	Refractory anemia	Erythrocytic hypoplasia	"Thymoma"*		Resection	No improvement
17. Fisher & Beyer (1958)	68	M	Pancytopenia	Hypoplasia, complete	Spindle cell		Transfusions	Died

* Not described.
† (?) our question.
‡ No picture for evaluation.

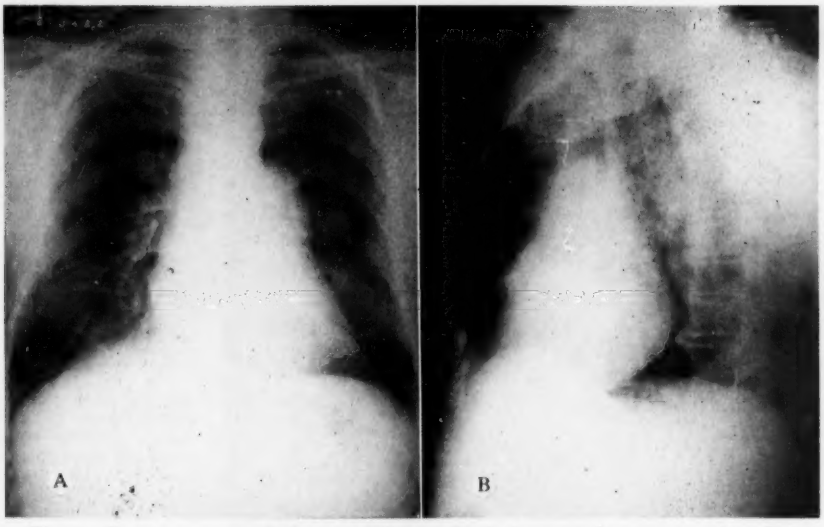


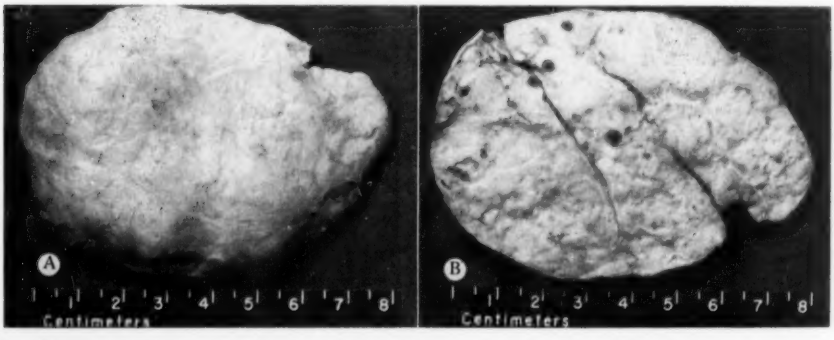
Fig. 1.—Roentgenograms of chest, revealing mediastinal mass. *A*, anteroposterior. *B*, left antero-oblique.

prolonged to 35 minutes. Prothrombin times were only slightly prolonged on rare occasion. Aspirations of bone marrow revealed generalized hypoplasia with immature granulocytic forms and a paucity of nucleated red blood cells and a very rare megakaryocyte. The myelocyte-erythrocyte ratio was estimated at 20-30:1. A marrow biopsy was unsatisfactory, Coomb's tests and L. E. preparations were negative, as were serologic tests for syphilis. Serum bilirubin ranged from 0.35 mg. to 2.0 mg/100 ml. Bile was not detected in the urine, and urobilinogen was 0.26 Ehrlich units. Serum protein determination revealed 3.9 gm. albumin and 2.0 gm. globulin. Other blood chemistry determinations and tests of liver function were within normal limits. Gastric analysis failed to reveal free acidity after the administration of histamine.

X-rays of the chest revealed a circumscribed rounded mass in the anterior mediastinum (Fig. 1). The remainder of the mediastinal structures appeared normal.

The patient's course was, for the most part, afebrile. A rise of temperature to 102 F accompanied by chills was noted occasionally following blood transfusions. No other manifestations of incompatibility were observed. During the last two weeks of life he displayed an intermittent fever, with temperature of 102 F. He received cyanocobalamin (vitamin B_{12}) and a total of 41 blood transfusions and packed red cells and platelets. Tetracyclene, oxytetracyclene, and penicillin

Fig. 2.—Outer surface of thymoma, revealing slightly bosselated encapsulated surface. *A*, cut surface of thymoma, disclosing homogeneous lobules of neoplasm separated by fibrous septa, *B*.



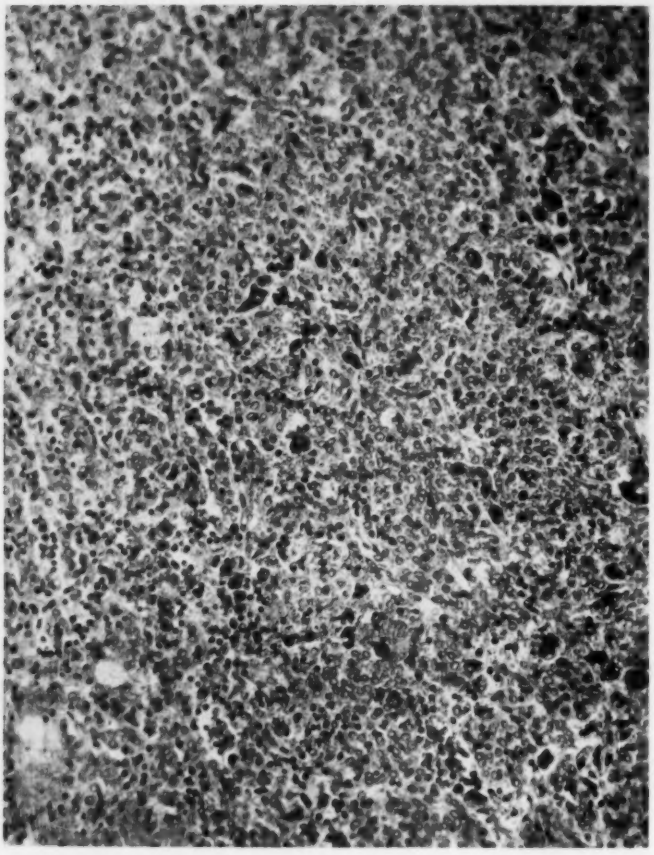


Fig. 3. — General appearance of thymoma, revealing marked cellularity. Some lymphocytes are scattered throughout the tumor; × 135.

were administered at various times during his hospitalization, and he received corticotropin (ACTH), 40 units per day, and prednisone, 40-60 mg. per day, for three months prior to death. However, his weight progressively declined and he exhibited an ingravescent course characterized by hematuria, hemoptysis, epistaxis, and purpura.

Autopsy

Macroscopic Findings.—Numerous petechiae were evident in the skin of the extremities and chest.

A circumscribed, encapsulated, firm, tan neoplasm, measuring 7×4 cm. and weighing 100 gm., was present in the anterior mediastinum in the region of the thymus. Its cut surface revealed lobules of homogeneous yellow-tan tissue separated by fibrous septa of varying thickness (Fig. 2). The neoplasm was not adherent to the sternum anteriorly and was readily separated from the pericardium and pleura. Normal thymic tissue was not recognized.

The combined weight of the lungs was 2600 gm. Their pleural surfaces contained a scant fibrinous exudate. Cut surfaces revealed marked edema and hemorrhage, more marked on the left. A large antemortem clot occluded the main branch of the left pulmonary artery.

The coronary arteries and aorta exhibited a moderate amount of atherosclerosis.

The spleen weighed 350 gm. It was firm and reddish-brown.

The vertebral and sternal bone marrow were pale.

The kidneys appeared normal except for the presence of petechiae in their pelves.

Microscopic Findings.—Sections of the tumor from the anterior mediastinum revealed a neoplasm comprised of ovoid and spindle cells, with relatively scant amphophilic cytoplasm and vesicular nuclei arranged in whorls. A few lymphocytes were scattered throughout (Figs. 3 and 4). Not infrequently this pattern was evident about simple

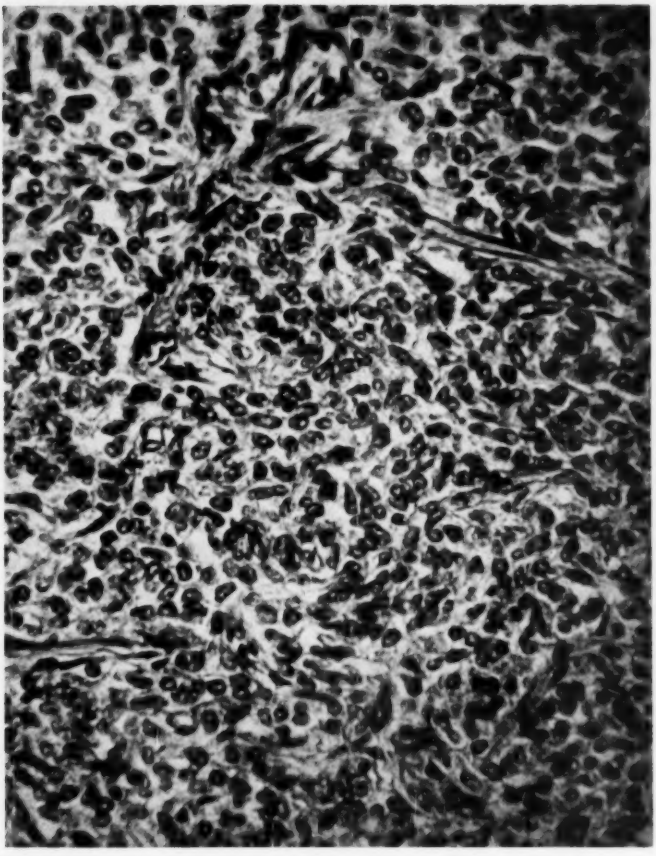


Fig. 4. — Spindle-cell nature of neoplastic cells is apparent; × 425.

endothelial lined spaces and small blood vessels, and in a few areas collections of neoplastic cells approximated large congested vascular spaces presenting an "endocrine pattern." The vascular pattern was more readily appreciated in sections stained by Wilder's reticulum method, which demonstrated the perivascular arrangement of tumor cells and the distribution of reticulum fibers about large groups and only rarely individual cells (Fig. 5). The tumor cells were uniform, without evidence of anaplasia. Mitoses were exceedingly rare. No cellular fibrils could be identified in sections stained with phosphotungstic acid hemotoxylin, and no intracytoplasmic Schiff-positive material was observed. Only an occasional cluster of lymphocytes was evident among the tumor cells, which were divided into lobules by fibrous septa of varying thickness. These latter contained round and elongated channels lined by simple endothelial-like cells as well as three and four layers of cuboidal forms. Their lumens contained an acidophilic coagulum, which occasionally was brilliantly colored by the periodic acid-Schiff technique (red-purple) and was resistant to diastase digestion (not glycogen). Similar channels were noted within the cellular elements of the neoplasm, which was completely surrounded by a fibrous capsule. No extension of the neoplasm into the capsule or its vessels was evident.

Sections of the lungs revealed marked congestion, alveolar hemorrhage, and edema. Bacterial masses were frequently observed, as well as fibrin masses. Neutrophils were inconspicuous in such areas, however. The clot in the main branch of the left pulmonary artery was comprised of laminated fibrin. Only slight reaction was apparent in the intima of the artery.

Sections of the spleen revealed congestion and hemorrhage into the pulp cords. Hemosiderin-laden macrophages were conspicuous in the latter. Plasma cells were abundant in this structure, as well as lymph nodes.

Sections of bone marrow from vertebrae and sternum were similar, revealing marked hypoplasia

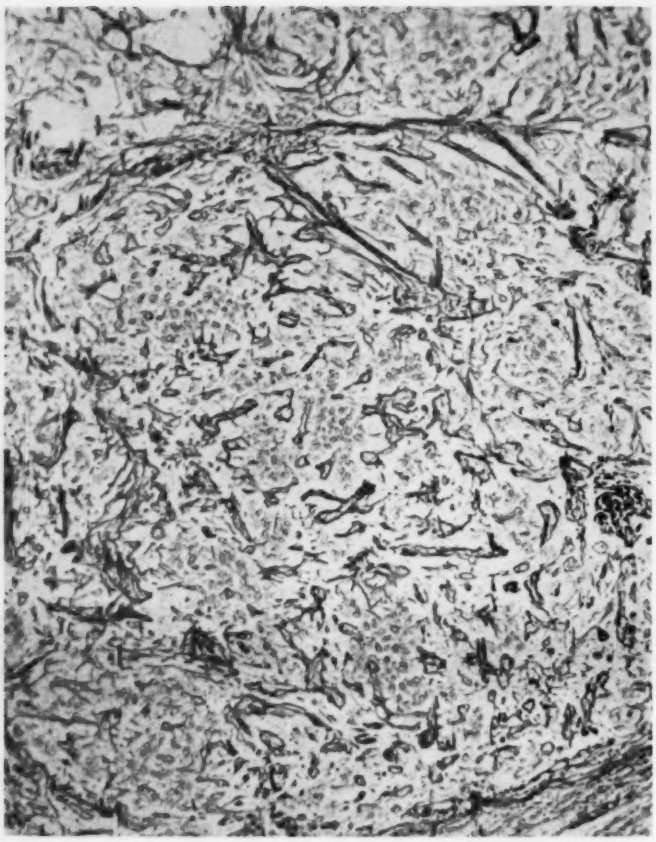


Fig. 5.—Section of neoplasm stained by Wilder's reticulum method, revealing extravascular postion of neoplastic cells, similar to that observed in hemangiopericytoma; × 135.

of all elements (Fig. 6). Only rare, immature, granulocytic, or erythrocytic elements could be identified, and only a few megakaryocytes could be found in the many sections studied. Occasional foci of lymphocytes and plasma cells were evident (Fig. 7).

Petechial hemorrhages were evident in the skin and renal pelves. The blood vessels of the skin morphologically appeared unaltered. The major diagnoses were (1) thymoma, spindle-cell type; (2) hypoplasia of bone marrow, complete (all elements); (3) pulmonary embolus, massive, left with pulmonary edema; (4) hemosiderosis, moderate, of spleen; (5) purpura, diapedesis type.

Comment

The association of pancytopenia with complete (all elements) hypoplasia of the bone marrow and thymoma as observed in this patient is unusual. Only 4 of the previously recorded 16 examples of this syndrome exhibited such a hemopoietic disorder, and in one[10] of these thymic hyperplasia rather than thymoma was evident. Most emphasis has been placed upon the presence of refractory anemia with aplasia of erythrocytic progenitors in the bone marrow. In one instance the anemia was considered to be of the pernicious type.[5] Although there is no convincing experimental or other evidence relating thymic function to hemopoiesis, certain considerations suggest that the relationship between thymic neoplasia and suppression of hemopoiesis is more than fortuitous. In at least two previous instances[6,13] the thymic neoplasm clearly antedated the blood dyscrasia. Improvement in hemopoietic function has been observed in five[9,11,13,17] of the eight patients in whom successful resection of a

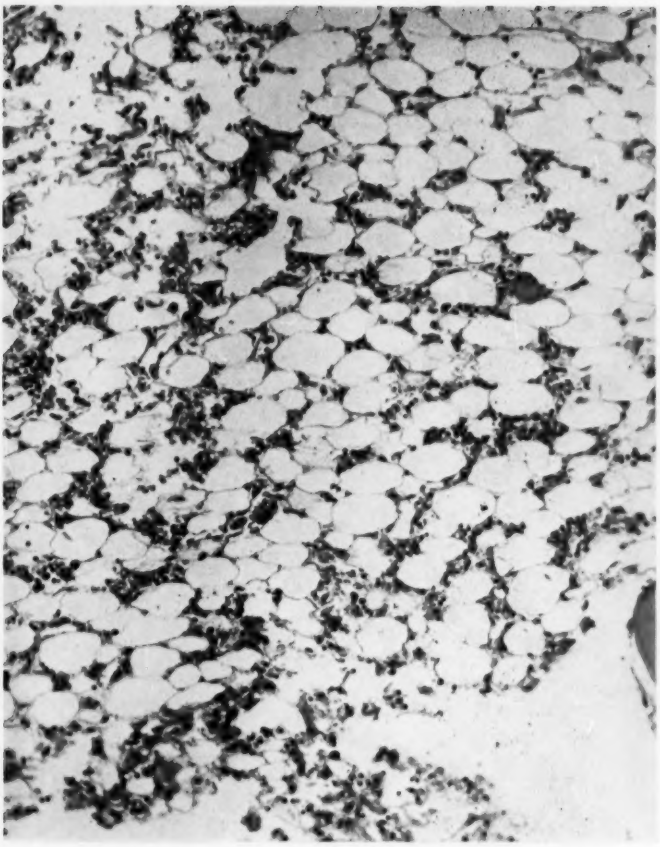


Fig. 6. — Severe hypoplasia of bone marrow with only few cellular elements; × 165.

thymoma has been performed. Spontaneous remissions from complete or incomplete marrow hypoplasia are infrequent.[21] The failures following thymectomy do not necessarily refute the significance of this observation. It is conceivable that irreparable marrow changes may occur, preventing a satisfactory response. The delayed response observed in several instances[7,15] suggests that death may result from intercurrent causes before sufficient time has elapsed for marrow regeneration. It is worthy of consideration that in some instances thymic remnants were overlooked at the time of operation. This possibility suggests that the thymus per se may be influenced by its neoplastic component to produce such an effect. Lastly, rarity of both thymoma and idiopathic hypoplasia of the bone marrow would suggest that their association is more than one of chance. The failure to obtain a history in this patient of exposure to chemical poisons or to find clinical or pathologic evidence of hypersplenism, endocrine disorder, or hemolytic anemia substantiates the primary nature of the hemopoietic disorder encountered. The relatively small amount of irradiation received by this patient appears insufficient to have produced such an effect.

It is generally appreciated that pathologic classification of thymic neoplasms is unsatisfactory and that there is a lack of agreement among pathologists concerning terminology. Because of this the relatively noncommittal term thymoma has gained

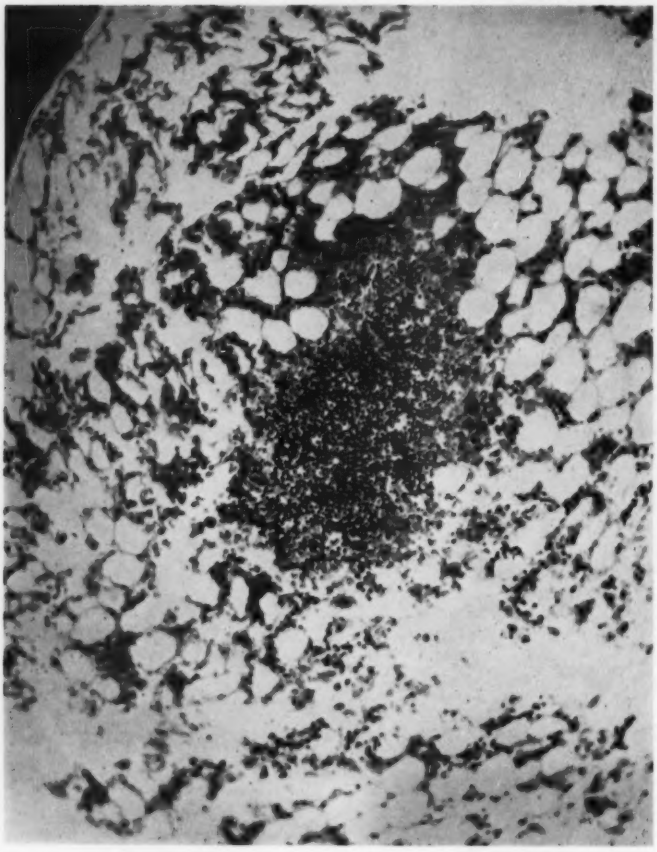


Fig. 7. — Lymphocytic aggregate in otherwise hypoplastic bone marrow; × 135.

popularity. However, with the renewed interest in these neoplasms stimulated by their recognition with various disease states it would appear mandatory that attention be directed to the morphologic variants encountered. Only in this manner may information be derived which will not only allow for more precise clinicopathologic correlations but also perhaps provide some insight into thymic function. It is of interest in this regard that those thymic neoplasms observed with Cushing's disease have been uniformly of adenocarcinomatous structure.[1] Review of the previously recorded examples of thymoma associated with refractory anemia or pancytopenia in which sufficient morphologic information was available has revealed the spindle-cell type of thymoma to be most frequent in this syndrome. The lesion in the patient of this report was also of this type. It is usually held that such neoplastic cells are epithelial in origin. However, it is noteworthy that the morphologic appearance of this tumor is compatible with that observed in hemangiopericytoma.[22] The lack of cellular fibrils in sections stained with phosphotungstic acid hematoxylin, absence of cellular glycogen, and distribution of reticulum about cell aggregates located about vascular spaces also are features consistent with this type of vascular neoplasm.[23] It is pertinent to note that Pope and Osgood [12] designated this type of thymoma as a reticular perithelioma and that Hubbell and Liebow [24] subscribed to its lymphangioendothelial origin, placing

much emphasis on transitions between the simple lined channels observed in the septa of the neoplasm and more solid areas. We have been unable to demonstrate to our satisfaction whether such channels are vascular or mesothelial in nature, as contended by Castleman, although the former interpretation may be considered in support of the vascular nature of this type of thymoma. If, indeed, the lesion is a hemangiopericytoma we know of no other example of this type of tumor in the mediastinum [25,26] or extramediastinal sites which has been associated with such a suppression of hemopoiesis. Massive hemangiomas in children have been reported associated with thrombocytopenia, but it has been considered that the latter is the result of the sequestration of platelets within the vascular channels of the neoplasm, as evidenced by platelet thrombi.[27] The latter were not encountered in the thymoma in this patient. It is of interest, however, that megakaryocytic arrest has been observed in the bone marrow in some instances. Whether this latter is the result of a deficient feed-back mechanism, as proposed, or some other cause would appear to merit further investigation. The above considerations indicate the need for more precise identification of this type of thymic tumor, as might be obtained by tissue culture. It is generally agreed that the malignancy of thymic neoplasm can be determined only by the presence of invasion of surrounding tissues and/or metastases. It has been indicated that thymomas associated with hemopoietic insufficiency are benign.[15] However, attention is called to the example recorded by Opsahl [7] in which invasion of the lung was apparent at necropsy.

Although the patient of this report exhibited a moderate depression of serum globulins, the ubiquitous occurrence of plasma cells would indicate that hypo- or agammaglobulinemia did not exist. Such cells are usually sparse or absent in patients with agammaglobulinemia, with or without thymoma.[28]

Summary

An example of a spindle-cell thymoma associated with complete marrow hypoplasia and pancytopenia in a 68-year-old white man is presented. Analysis of 16 previously recorded examples of a thymic neoplasm or hyperplasia and hemopoietic insufficiency are reviewed. Although absolute proof that the latter is directly caused by the thymic neoplasm is lacking, certain considerations suggest such a relationship.

Attention is directed to the histological similarities of the spindle-cell thymoma, which appears to represent the most frequent type of thymoma in this syndrome and hemangiopericytoma.

The recognition of the association of thymoma with hypoplasia of the bone marrow manifest as refractory anemia or pancytopenia appears mandatory, since thymic resection has contributed to the clinical improvement of two-thirds of the patients in whom such a procedure was successfully performed.

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Thrombotic Thrombocytopenic Purpura

Two Patients with Remission Associated with the Use of Large Amounts of Steroids

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In 1954, Singer reviewed the subject of thrombotic thrombocytopenic purpura, collecting 55 cases from the literature.[1] Wile and Sturgeon, in 1956, compiled an additional 19 instances and added 3 case reports in children.[2] We are aware of an additional 25 reports during the years 1954-1957, bringing the total number of cases to over 100.[3-27] In general the clinical course of this disorder has been most unfavorable, the majority of patients dying within eight weeks of the recognized onset of the disease. In rare instances survival for more than one year has been reported.[23,24,26,28,29] Several of these patients had atypical manifestations, so that it is difficult to ascertain the time of onset of the disease and the survival time in all of these cases.

No well-documented typical case has undergone long-term spontaneous remission, and a variety of therapeutic endeavors has in general failed to influence the course of the disease. There have been no prolonged remissions reported following the use of corticotropin (ACTH) or steroids alone, but in four instances temporary improvement did take place, lasting for 36 days in one patient [10] and for 13 days in another.[28] The other two patients received steroids, improved, and were then splenectomized.[26,29] Only one remission longer than one year has followed splenectomy alone.[28]

Four patients have remitted following treatment with both steroids and splenectomy.[23,24,26,29] On the other hand, splenectomy and steroids or corticotropin alone or in combination have apparently failed in most reported cases (e. g., references 1-7, 10,15-21,25,27-35). In most instances the amount of steroid employed was not large, and frequently the use of these drugs was restricted to the last few days of life. The present report documents two cases with long-term and continuing remission following the use of *large* amounts of steroids.

Report of Cases

CASE 1.—A 26-year-old white farmer was admitted to the Vanderbilt University Hospital in a confused and disoriented state on June 17, 1955. Three years prior to admission he experienced temporary loss of consciousness but no other obvious sequelae following an automobile accident. From 1953 to the time of admission there were several attacks of syncope. Otherwise the patient had been in excellent health until the sudden onset of frontal headache, "tingling" paresthesias of the right arm, and weakness of the right side of the body three weeks prior to admission. Within 24 hours he became asymptomatic and returned to work.

Ten days before admission there had occurred an episode of dysarthria, confusion, numbness of the face, weakness of the extremities, and vomiting of a small amount of blood. These manifestations lasted but 12 hours, and the patient continued to work despite subsequent repeated occurrence of acroparesthesias lasting 1-60 minutes. His associates noted "yellow eyes." Two days before admission there was another attack of confusion, "tremors all over," dysarthria, numbness and weakness of the extremities, and vomiting of a small amount of bright red blood. Easy bruising was first noted at this time. There was no history of recent respiratory infection, fever, allergic state,

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or immunizations. Ten days before admission the patient had been given a sulfonamide of unknown type and amount for approximately 48 hours. The family history was not remarkable.

The patient was confused and periodically disoriented and complained of dizziness and frontal headache. His gait was abnormal, with staggering to the left. These manifestations waxed and waned during the course of the initial examination and the ensuing few hours. The temperature was 98.6 F, and the respirations, 18 per minute. There was pallor of the skin and mucous membranes and moderate icterus of the sclerae. Scattered petechiae and ecchymoses were present over the chest and extremities and on the buccal mucosa. Funduscopic examination revealed no abnormalities. The pupils were dilated but reacted to light.

Examination of the lungs and heart was nonrevealing. The pulse was 96, and the blood pressure, 120/60. The liver, spleen, and kidneys were not palpable. Objective neurological findings were confined to the presence of a Babinski sign on the left and an accentuated left patellar tendon reflex.

The serological test for syphilis was negative. Urinalysis revealed 1+ proteinuria, 2-3 RBC per high-power field, urobilinogen positive in 1:20 dilution, and absence of bile. Initial blood cell counts were as follows: WBC 5500, normal differential count except for 9% neutrophilic juveniles, volume of packed red cells 22%, hemoglobin 7.0 gm. per 100 ml., RBC 2,400,000, sedimentation rate 65/18, reticulocytes 16.6%, and platelets 10,000. Examination of the blood smear revealed marked anisocytosis and poikilocytosis, moderate polychromatophilia, a few stippled and target cells, and 2 nucleated red cells per 100 white cells. The serum bilirubin was 2.8 mg. % total, with 2.3 direct.

The following blood chemistries were normal: fasting blood sugar, total protein, albumin-globulin ratio, alkaline phosphatase, cephalin flocculation, thymol turbidity, serum electrophoretic pattern, calcium, inorganic phosphorus, sodium, potassium, CO_2, and chloride. Sulfobromophthalein retention was 10%. The NPN was 38 mg. % on admission, rose to 77 on the 13th hospital day, and then fell to normal. Antistreptolysin O titer was 83 units.

Fecal urobilinogen was 2300, 2350, and 1310 Ehrlich units per 100 gm. in three separate specimens collected during the first four days of hospitalization. Direct and indirect Coombs tests were negative. A complete examination for evidence of autoimmune hemolytic disease was negative.* Repeated L. E.-cell tests were negative. Urine was negative for porphobilinogen and uroporphyrins. Osmotic fragility test was positive, with patient's cells showing "beginning hemolysis" in 0.66% sodium chloride solution and the control cells in 0.45% solution. Mechanical fragility was 3.9% (normal <3.0%). Bone marrow aspiration smears showed an increased proportion of pleomorphic megakaryocytes, many of which showed bizarre nuclear mitoses and dark blue immature cytoplasm. No apparent "platelet production" was seen. The proportion of erythroid cells was 32.4%.

Bleeding and clotting times were prolonged. Capillary fragility was markedly increased. Plasma prothrombin activity and fibrinogen concentration were normal. The abnormal prothrombin utilization was corrected by the addition of washed normal platelets. Tests for circulating anticoagulant and for evidence of increased fibrinolytic activity were negative. Twenty-four-hour urinary excretion of serotonin was within normal limits.

Spinal fluid revealed no cells and a protein value of 86 mg. %. Electroencephalogram revealed a pattern suggesting "diffuse cortical abnormality." Electrocardiogram was within normal limits. Serial section of a skin and muscle biopsy specimen from the gastrocnemius region revealed no vascular or other abnormalities.

The hospital course was striking (Fig. 1). On the second hospital day the patient was started on cortisone acetate, 300 mg. orally per day, and during the first week received 3000 ml. of whole blood. Several new petechiae appeared, and episodic confusion, dizziness, paresthesias, and vomiting persisted for the first four days but then disappeared and have not recurred since. Low-grade fever was present during the first nine days. On the 11th day of therapy reticulocytes fell temporarily to 2.9%, but no significant response in hematocrit or platelets had occurred.

On the 13th treatment day hydrocortisone,† 140 mg. daily by mouth, was substituted for the cortisone acetate and the patient was discharged improved, to be followed in the outpatient department. One week later (20th steroid-treatment day) the platelet count was 53,000, and thereafter the hematocrit rose and the reticulocytes fell to normal. Hematological improvement continued. Fecal urobilinogen, icteric index, sedimentation rate, blood smear abnormalities, osmotic fragility, and hemostatic function tests all returned to normal within the ensuing several weeks. Electroencephalogram still showed "diffuse cortical abnormality" on Aug. 8, 1955, but was normal thereafter. The dose of hydrocortisone was progressively reduced, and finally this drug was discontinued in October, 1955.

The patient has remained entirely asymptomatic and has worked regularly. He was readmitted in

* These tests were performed by Dr. Milton Sacks and Miss Elsa Jahns, of the Baltimore Rh Typing Laboratory.

† Cortril was supplied by the Pfizer Laboratories, Brooklyn.

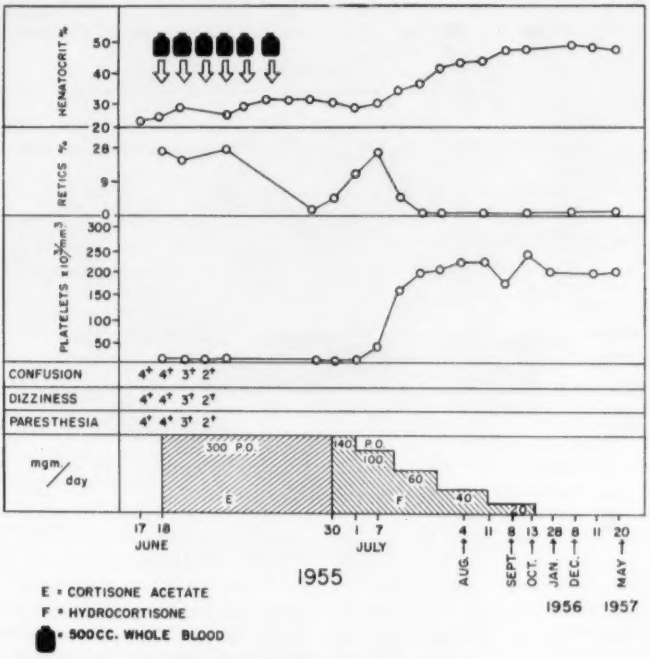

Fig. 1.—Clinical course in Case 1.

December, 1956, for complete reevaluation. All studies were normal. Our last contact with the patient in February, 1958, revealed that he was entirely asymptomatic and was working as a day laborer in Florida.

CASE 2.—A 50-year-old white postal clerk was first admitted to St. Thomas Hospital on Jan. 15, 1957, complaining of recurrent episodes of dizziness. Thirteen months prior to admission he experienced two attacks of weakness and dizziness without loss of consciousness. These symptoms cleared spontaneously within 20 minutes and were attributed to overwork due to the "rush of the Christmas season." Three similar attacks occurred during the following year.

Again, while sorting mail during the "1956 Christmas rush," he experienced an attack of syncope which was accompanied by dysarthria, "tingling" paresthesias in both hands, "swollen feeling" in the region of the hard palate, mental confusion, inability to use his arms, and facial paralysis. These attacks recurred several times during the next three weeks, usually lasted but 30-45 minutes, and were followed by mild frontal headache and somnolence of a few hours' duration. Six days prior to admission the patient experienced an episode of confusion and dysarthria lasting 48 hours. At this time he noted dark urine. His physician informed him that his hemoglobin value had fallen 50% over a four-day period. Increasing weakness and slurred speech brought about hospitalization. The patient had had a left midthigh amputation necessitated by shrapnel injuries in World War II. The family history was not remarkable.

The patient was a confused white man who appeared acutely ill. The speech was slurred, and a right lower facial weakness was present. The temperature was 99.4 F, and the respirations, 20 per minute. There was pallor of the skin and mucous membranes. The sclerae were not icteric. There were a few scattered petechiae and ecchymoses on the trunk and extremities. Funduscopic examination revealed no abnormalities. The examination of the heart and lungs showed normal findings. The pulse was 104, and the blood pressure, 130/78. No abdominal organs or masses were palpable. Objective neurological findings were confined to the evidence of an inconstant right facial weakness.

Serological test for syphilis was negative, as were repeated urinalyses. Admission blood cell counts revealed the following information: volume of packed red cells 24%, hemoglobin 6.7 gm. per 100 ml., WBC 13,500, normal white cell differential count, platelets 40,000, and reticulocytes 6.5%. Total serum bilirubin varied between 0.9 and 1.8 mg. %. The following tests gave normal results: NPN, total serum protein, albumin-globulin ratio,

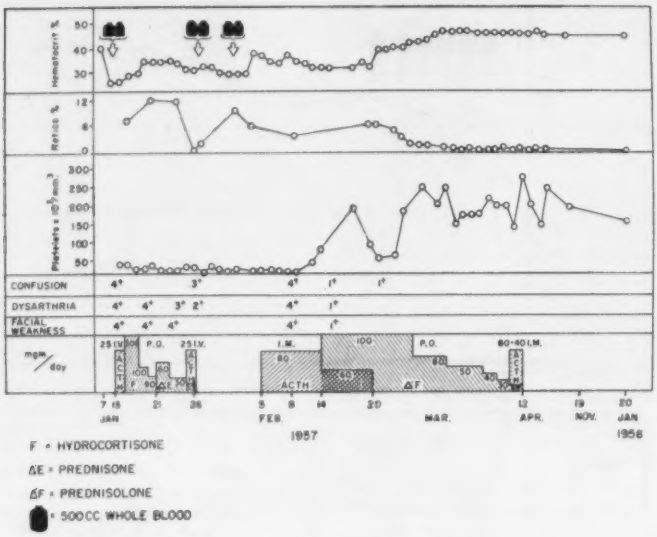

Fig. 2.—Clinical course in Case 2.

chest x-rays, occult blood in stools, direct Coombs test, osmotic fragility test, and repeated L. E.-cell tests. The bleeding time was 8 minutes (Ivy method), and the clotting time (Lee-White), 10 minutes. The Rumpel-Leede tourniquet test was positive. Bone marrow aspiration smears showed an increased proportion of megakaryocytes without discernible "platelet production." The proportion of erythroid cells was 54%.

The patient was treated with whole-blood transfusions, corticotropin, and later steroids (Fig. 2). He received a total of 3000 ml. of blood and varying amounts of steroids during the next three weeks. The volume of packed red cells rose to approximately 35%, but there was no change in platelet count. The episodes of confusion, dizziness, dysarthria, paresthesias, and right facial weakness persisted. Low-grade fever was present during the first two weeks. On the 20th hospital day the patient experienced a severe epistaxis. A skin and muscle biopsy was reported as normal.

The patient was transferred to the Thayer Veterans Administration Hospital on Feb. 8, 1957. Physical findings were unchanged. The volume of packed red cells was 35%, platelets 6000 and serum bilirubin 1.2 mg. %. Cerebrospinal fluid and liver-function tests were normal. Electroencephalogram showed a left anterior temporal abnormality (slow waves).

Three hours after admission the patient had another episode of confusion, dysarthria, left lower facial weakness, and paresthesias, with loss of pain sensation in both arms and hands. These symptoms and signs disappeared within 30 minutes. Corticotropin, 80 mg. intramuscularly per day, was continued. During the next week there were five similar episodes, one accompanied by generalized convulsions. On Feb. 14 (seventh hospital day) the patient was started on prednisolone,‡ 100 mg. per day by mouth. Within 36 hours there was dramatic neurologic improvement; dysarthria and facial weakness disappeared; attacks of mild confusion persisted, however, for two weeks. The platelet count showed a temporary rise to 198,000. Without further blood transfusions the volume of packed red cells gradually rose and the reticulocyte count fell.

On Feb. 20 the patient was transferred to Vanderbilt University Hospital. On admission he was afebrile and normotensive. He complained of tight facial skin. The face was moderately plethoric and rounded. A few scattered old ecchymoses were noted on the trunk and extremities. The liver was palpable 4 cm. below the right costal margin. No neurological abnormalities were detected.

Initial blood cell counts revealed the following information: WBC 11,900, "shift to the left" in differential count (undifferentiated myelocytes 2%, differentiated myelocytes 7.5%, juveniles 8.5%), volume of packed red cells 34.5%, reticulocytes 6.2%, and platelets 76,000. Examination of the blood smear revealed slight poikilocytosis and polychromatophilia. Total serum bilirubin was 0.6 mg. %.

‡ Prednisolone, 100 mg. tablets, was supplied by Dr. Robert W. Talley, The Upjohn Company, Kalamazoo, Mich.

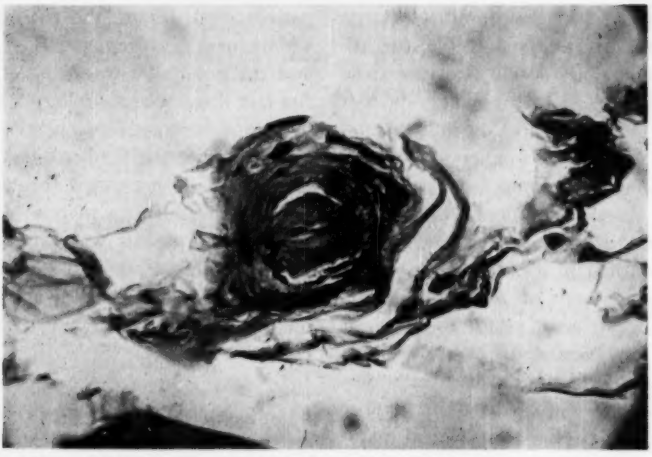

Fig. 3.—One of the "platelet thrombi" in the marrow biopsy wound in Case 2.

A complete examination for evidence of autoimmune hemolytic disease was negative. L. E.-cell and urine serotonin tests were negative. Mechanical fragility was 3.6% (normal <3.0%). Osmotic fragility test was negative when performed on fresh red cells. After sterile incubation of blood at 37 C for 24 hours, the patient's cells showed "beginning hemolysis" in 0.63% sodium chloride solution; the control value was 0.54%.

The clotting time was normal. The bleeding time was 12½ minutes (Ivy method), and clot retraction, 64% (normal >70%). Capillary fragility and prothrombin utilization were normal. "Touch" smears from an iliac crest biopsy revealed cellular marrow and rare megakaryocytes without evidence of "platelet production." The proportion of erythroid cells was 18.5%. The marrow sections failed to reveal any abnormalities of the cellular pattern of the marrow or any discrete blood vessels. A few hyalinized thrombi were seen in the skeletal muscle biopsy obtained from the iliac crest biopsy wound (Fig. 3). This specimen was obtained on the ninth day of therapy with 100 mg. of prednisolone and approximately five weeks after initial steroid and corticotropin therapy was instituted. Electrocardiogram revealed ST segment depression in limb Leads II and III and Lead aV_F. Electroencephalogram was again interpreted as indicative of a left anterior temporal abnormality.

The patient was continued on prednisolone, 100 mg. orally per day, and corticotropin was discontinued. Testosterone cyclopentylpropionate, 400 mg., was given intramuscularly every two weeks in an attempt to minimize tissue wasting. The patient continued asymptomatic except for the complaint of tight facial skin. The volume of packed red cells and platelet count rose to normal values, and the reticulocyte count fell to normal.

Weekly electroencephalograms showed persistence of the mild left anterior temporal abnormality through March 29, 1957. The recording on April 5, 1957, was normal. The dose of prednisolone was gradually decreased and finally discontinued on April 12, 1957, concomitant with corticotropin therapy for six days. The patient has been asymptomatic since and is now working regularly. When last seen, in January, 1958, approximately 13 months after the onset of acute manifestations, his only complaint was the occurrence of mild temporary paresthesias of the thumbs and index and middle fingers while shaving. The physical examination, blood cell counts, and ECG were normal. Electroencephalogram showed questionable evidence of left anterior temporal abnormality.

Comment

Two cases of thrombotic thrombocytopenic purpura with prolonged remission following the use of large amounts of steroids have been presented. Although in Case 1 biopsy proof was not available, in both cases the classical triad of thrombocytopenic purpura, hemolytic anemia, and bizarre episodic neurological changes was present.[1] Low-grade fever was present in both cases initially. The results of laboratory studies were compatible with this diagnosis and failed to reveal any evidence of associated disease. There were no peculiar or complicating features.

Absolute proof that the steroids in large amounts were directly responsible for inducing the remissions is not available. The sequence of events, however, suggests that the therapeutic regimen had an influence on the disorder in these two patients. In Case 1 the neurological symptoms disappeared after four days' treatment with *large* amounts of cortisone, and the blood picture returned to normal in less than one month. In Case 2 one month of sporadic therapy with corticotropin and small amounts of steroids did not greatly influence the blood picture or neurological manifestations. When prednisolone was started in a dose of 100 mg. per day, the neurological manifestations improved promptly and disappeared completely within one week. The blood picture became normal within two weeks. In Case 2 the recent return of mild paresthesias of the fingers and of a questionable electroencephalographic abnormality suggests that the disease process may still be smoldering.

The only discernible side-effect of the large doses of steroids was mild acneiform rash in one patient and moderate facial rounding in both. Rigid sodium restriction and potassium supplementation were utilized.

Increasing interest in any disorder leads to recognition of less severe forms of the disease. Perhaps these are instances in which the use of *large* amounts of steroids merely prevented a fulminant downhill course and allowed sufficient time for spontaneous remission to occur. More specifically, these two cases may represent less severe forms of thrombotic thrombocytopenic purpura which, as such, are responsive to therapy with *large* amounts of steroids. Smaller amounts of steroids have had little influence on the rapidly fatal course of this disorder. There is no intention to imply that the use of *large* amounts of steroids will result in remission in all cases or at all times. Four patients have died after two to six days of therapy with 300 mg. or more of cortisone per day.[15,16,18] Another patient died despite the use of prednisone (Meticortin), 60 mg. per day for 18 days, and cortisone, 300 to 1200 mg. per day for the last three weeks of life.[21] Recently, the use of hydrocortisone hemisuccinate, 600 mg. intravenously daily, failed to influence the course of presumed thrombotic thrombocytopenic purpura in one Vanderbilt patient. This patient was admitted in coma and died in 48 hours. (Permission for postmortem examination was not obtained, but the classical diagnostic triad was present.)

It is of interest that in both Case 1 and Case 2 there was a history of attacks of syncope during the year or two preceding the onset of the severe acute manifestations. This symptom is, of course, difficult to evaluate. In this respect another Vanderbilt case is of considerable interest. In May, 1952, this 45-year-old white man was studied because of several episodes of confusion and irrational behavior. Neurological examination, blood cell counts, and cerebrospinal fluid values were normal. Psychological testing, however, was suggestive of organic brain damage, and electroencephalogram revealed "episodal type of generalized cortical dysfunction without evidence of a focus." Thereafter, the patient was completely asymptomatic until May, 1954, when he developed typical fulminant manifestations of thrombotic thrombocytopenic purpura. Splenectomy and corticotropin and cortisone therapy (400 mg. daily of the latter for the last six days of life) were without discernible influence on the disorder. Because of an alleged superficial similarity between "platelet thrombi" and the lesions of the Shwartzman reaction[1] and because nitrogen mustards can block the Shwartzman reaction,[36,37] this drug was given as a last desperate measure. It, too, failed to influence the fulminant course of the disease. The diagnosis was proved by skin and muscle biopsy at splenectomy and the presence of widespread microscopic lesions at autopsy. These observations suggest that the prodromata of thrombotic

thrombocytopenic purpura may extend over a long period. Similar observations have been made by others.[1,5,26-28,31]

Conclusions

Two patients with thrombotic thrombocytopenic purpura experienced prolonged and continuing remission following the use of *large* amounts of steroids. Although in one case biopsy proof was not available, the clinical manifestations were classical. While it is impossible to prove that steroids directly brought about the remissions, the early use of *large* amounts of steroids may at least prevent certain cases from progressing to a fulminant downhill course. Such therapy is strongly recommended.

Addendum

Both patients were seen in August, 1958. They are asymptomatic and working regularly. Physical examination and blood counts were normal. Case 2 no longer experiences paresthesias of the digits while shaving. For Case 1 the time interval from the onset of acute symptoms is now 38 months, and for Case 2, 20 months.

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Bronchiectatic Destroyed Lobe as a Complication of Intrathoracic Goiter

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The main clinical features of intrathoracic goiter depend on the development of pressure effects on the various neighboring structures. The different effects of pressure in the mediastinum by intrathoracic goiter are listed in the Table.

Pressure Effects of Intrathoracic Goiter on the Neighboring Structures

Organ Compressed	Symptoms or Syndrome	References
Trachea	Stridor, acute dyspnea	2-5, 9
	Fatal strangulation	1, 2
Bronchus	Atelectasis	14, 15
Esophagus	Dysphagia	3, 5, 9
	Erosion	6
Superior vena cava	Superior vena caval syndrome	7, 8
Internal jugular veins	Dilatation of superficial thoracic veins, engorgement of neck veins, & edema of face	9
Innominate veins	Bilateral recurring hydrothorax	10
Thoracic duct	Chylothorax	11
Recurrent laryngeal nerve	Paralysis of vocal cord	4, 5, 12
Phrenic nerve	Paralysis of diaphragm	13

Pressure on the trachea causing stridor or acute dyspnea is a frequent condition. On the other hand, compression and obstruction of a bronchus with resulting atelectasis is rarely noted, and only two reports mentioning this condition have appeared. Falor et al. described a case in which a retroaortic goiter caused pressure on the right intermedius bronchus, resulting in transitory atelectasis of the middle and lower lobe.[14] Four of Hoffman's thirty-two patients with intrathoracic goiter had radiographic evidence of segmental or lobar atelectasis on admission; however, no details of these cases are given. The following case represents what is believed to be the first reported instance of pulmonary fibrosis with cystic bronchiectasis due to bronchial obstruction by intrathoracic goiter.

Submitted for publication March 14, 1958.

From the Department of Chest Diseases, Rothschild Hadassah University Hospital.

Report of Case

A 64-year-old Czech-born woman was admitted on Nov. 19, 1956. Her brother was said to be suffering from toxic goiter. In 1945, when she was liberated from a Nazi concentration camp, routine roentgenography disclosed some abnormality of her right lung. As her sputum was negative for tubercle bacilli, she was told that she had had pulmonary tuberculosis in the past. In 1950, on routine roentgenography after immigrating to Israel, fibrosis of the right upper lobe was found. Cultures of sputum were again negative for tubercle bacilli. In 1952, following a sudden copious hemoptysis, she was hospitalized for three months in a tuberculosis hospital. In 1953, she underwent mastectomy because of cancer of the left breast, followed by x-ray therapy to the left axilla. In 1956, she developed a cough associated with mucopurulent sputum and low-grade fever. She was admitted to another tuberculosis hospital and after three months was transferred here for further investigation.

On admission, the patient was afebrile and in fair general condition. Her complaints were moderate cough, with 15-20 cc. of sputum; tremor of the hands; sweating, and falling hair. On physical examination the eyes were normal. The thyroid appeared to be only slightly enlarged, but although it rose on swallowing, it was not possible to palpate its lower pole. The pulse was 84 per minute and regular, and the blood pressure was 165/85. The first sound over the aortic area was accentuated. Over the right upper half of the chest medium-sized rales were heard anteriorly and posteriorly.

The erythrocyte and leukocyte counts and urine analysis were normal; the serum cholesterol was 200 mg. %; the ECG, normal, and the basal metabolic rate, +55%.

Radiography and particularly the tomographic studies (Figs. 1 and 2) showed a 4×4 cm. tumor

Fig. 1.—Intrathoracic goiter lying on the right side of the mediastinum.

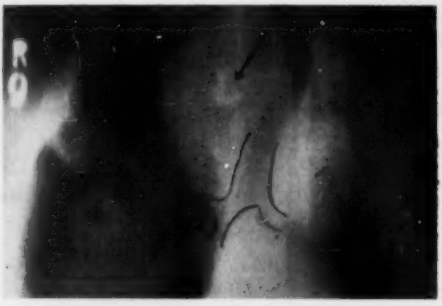

Fig. 2.—Obstruction of the right upper bronchus and compression of the right upper lobe by goiter. Displacement of the trachea toward the left. Calcification of the body of the goiter (anteroposterior tomography, layer 9 cm.).

with smooth outlines lying on the right side of mediastinum, displacing the trachea toward the left. There was a soft amorphous calcification in the body of tumor. In the tomographic 7 cm. layer compression of the right upper bronchus as well as compression of the right upper lobe by the inferior pole of the tumor was clearly visible (Fig. 2). On lateral tomography the right upper lobe was seen to be full of large bronchiectatic sacs, separated by condensed fibrotic tissue (Fig. 3). On fluoroscopy the tumor moved with swallowing and no pulsation was observed.

Studies with I^{131} showed two areas of increased uptake on the superior pole of the left lobe of the thyroid and in the right parasternal region. The level of protein-bound radioactive iodine in the plasma and the excretion of I^{131} both in the urine and the saliva clearly indicated hyperactivity of the thyroid.

The patient was considered to be too poor a risk for surgical intervention (thyroidectomy and lobectomy). After treatment with strong iodine (Lugol's) solution and antibiotic drugs her condition improved markedly, and she was discharged two months after admission.

Fig. 3.—Right upper lobe full of bronchiectatic sacs and showing extensive destruction (right lateral tomography, layer 7 cm.).

Summary

A case of pulmonary fibrosis with cystic bronchiectasis due to obstruction of the bronchus by a toxic intrathoracic goiter is presented. This appears to be the first reported case of this complication of mediastinal struma.

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Lethal Midline Granuloma of the Face

Report of Case and Review of the Literature

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Introduction

Lethal midline granuloma was first described by McBride,[1] in 1897 and is rare. It occurs rarely below the age of 20 and is almost nonexistent in females, with the sex ratio being reported by Woodburn and Harris [2] as 20:1.

Although the clinical course is typical, the diagnosis of lethal midline granuloma can be made only by exclusion. Approximately 100 cases have been reported in the literature. Only 50% of these were autopsied, and many did not have histologic examination of all organs and complete laboratory studies.

The diagnosis is frequently confused with syphilis, tuberculosis, neoplasms, and fungus diseases.

Report of Case

A 35-year-old white male postal clerk was admitted to the Philadelphia Veterans' Administration Hospital on Feb. 7, 1957, with a large ulcerated lesion involving the left side of the nose and a large part of the left cheek, associated with marked edema of surrounding areas.

The patient had been well except for a history of slight intermittent nasal congestion for several months, until August, 1956, at which time he first noted a nontender "pea-sized lump" on the lower lateral aspect of the left nasal ala. After five weeks, owing to moderate enlargement of this lesion, the patient consulted his family physician, who treated him with daily penicillin injections for three days, followed by a five-day course of novobiocin (Albamycin), with no effect. By Oct. 16, 1956, this lesion had ulcerated and involved the upper lip area, lower borders of both nasal alae, and the lower part of the nasal septum (Fig. 1).

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Fig. 1.—Early stage in growth of lesion prior to hospitalization.

At this time, findings on biopsy of this lesion were reported as gummatous tertiary syphilis. Although repeated serological tests for syphilis were negative, the patient was treated with bismuth and penicillin injections.

After this therapy, marked improvement and healing of the primary lesion was noted. However, a small ulcerated area was noted higher in the left side of the nasal septum, from which there was purulent drainage. On repeat biopsy of this new lesion a diagnosis was made of either tertiary syphilis or some type of phagedenic ulcer with pyoderma. Smears, cultures, and guinea pig inoculations of the exudate were negative for tuberculosis. At this time, novobiocin, to which drug the organisms grown on routine cultures were sensitive, was given for a period of 10 days.

On Dec. 11, 1956, the lesion of the nasal septum was noted to be healing, and another course of bismuth tablets and injections was given over a period of a few weeks.

During the next eight weeks, immediately prior to hospitalization, the above areas of involvement became progressively larger and markedly ulcerated, despite the use of various oral antibiotics and local therapy. There was associated anorexia, moderate weight loss, and, in the three weeks prior to hospitalization, almost daily fever and chills.

Fig. 2.—Shortly after hospitalization, prior to therapy.

Physical examination on admission revealed a well-developed well-nourished-appearing white man in no acute distress, with temperature 100 F, pulse 100 per minute, and B. P. 125/80. The positive physical findings were limited to the face. There was a large 4.5×4.5×3 cm. ulcerated area involving the left lateral aspect of the nose (with marked destruction of its cartilaginous portion) and the left cheek, extending from the malar area to the supraoral region, with brown crusting in the base of the lesion and several actively discharging purulent areas. There was associated marked edema of the left side of the face surrounding this lesion from the infraorbital area to the angle of the

Fig. 3.—Following initial three weeks of massive antibiotic therapy.

mandible (Fig. 2). Lymphadenopathy, local or distant, was conspicuous by its absence in this case throughout most of the hospital course.

Laboratory Data.—White blood cell count and differential count on several occasions during hospital course were always within normal limits except for occasional mild lymphocytosis. Hemoglobin reached a low of 9 gm. during the latter stages of the disease. Urinalysis, blood serology, blood urea nitrogen, fasting blood sugar, serum protein, and complete spinal fluid studies were all normal. No spirochetes were found on dark-field examination of the facial lesion. Several cultures of this area showed α-hemolytic Staphylococcus pyogenes var. aureus and α-hemolytic streptococcus, which were considered to be nonspecific contaminant type organisms for this location. No fungi or acid-fast organisms were found. Several blood cultures were negative. P. P. D. No. 1 was negative, and P. P. D. No. 2 was positive (2+).

X-ray examinations of skull, sinuses, and left mandible throughout the hospital course showed only a left maxillary sinusitis and minimal ethmoidal involvement but no bony abnormalities. Chest x-ray was normal.

Course in Hospital.—Because of its diagnostic and therapeutic problems, the case was presented to the Philadelphia Dermatologic Society on Feb. 16, 1957, at which time there was a varied opinion among several prominent dermatologists as to the diagnoses of this lesion. The most popular diagnoses were (1) von Wegener's granulomatosis, (2) midline granuloma of the face, and (3) "malignant" type of pyoderma, etiology unknown.

Owing to the divergence of opinions as to diagnosis of this lesion prior to and during hospitalization, a biopsy was performed on Feb. 22, 1957. Histologically it showed extensive tissue necrosis, considerable pseudoepitheliomatous hyperplasia, inflammatory changes with arteritis, and the presence of clumps of intermediate mononuclear cells which were very suggestive of malignant lymphoma. (The latter finding was not consistent in all areas.) Special stains failed to identify any etiologic agent. With the knowledge of the clinical picture, the pathologist felt that these nonspecific histologic changes were consistent with gangrenous ulcer of the midline facial tissues.

A course of therapy with massive doses of various antibiotics (penicillin, streptomycin, chloramphenicol [Chloromycetin], novobiocin, and tetracycline [Achromycin]) in various combinations was carried out, with only transient effect in decreasing the temperature elevations (Fig. 3). Even with the addition of repository corticotropin injection (ACTH gel), 80 units per day, and prednisone (Meticortin), the ulcerated lesion continued to grow in size. Also, the use of various local antibiotic solutions (neomycin and bacitracin) and Debricin, a new local chemical proteolytic debriding agent, seemed only to increase swelling surrounding the lesion. Despite the growth of the pathological process accompanied by almost daily temperature elevation, the patient felt relatively well. X-ray therapy was then instituted (100 r every other day) but was stopped after a few days because of continued progression of the lesion.

On March 15, 1957, because of the failure of the above-mentioned treatment to halt the progress of the lesion, a radical excision with wide surgical debridement of the ulcerated area was done, with secondary skin grafting afterward. Removed at this time was three-fourths of the nose and the left molar bone and maxilla. Histologic examination of these tissues showed no change from previous biopsy. This surgical procedure, followed by supportive therapy (including several blood transfusions and tube feeding for a few days) and the use of antibiotics and steroids (in similar dosages to those prior to surgery) seemed to arrest the process. There was marked healing of the operative site, no exudation, and decreased swelling of the facial tissues. During the next six weeks the patient had a good appetite, felt well, was completely afebrile for the first time since admission, and gained approximately 20 lb. However, the patient was still maintained on steroid and antibiotic therapy.

On May 1, 1957, a new area of involvement was noted, with swelling over the left mandible. On June 3, 1957, ulcerated areas were noted inside the mouth and on the left mandibular area exter-

Fig. 4.—Post mortem.

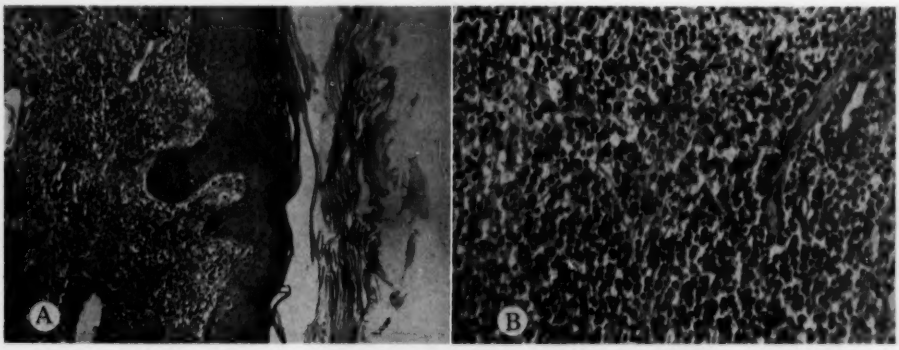


Fig. 5.—Sections from original biopsy of nasal lesion, October, 1956, showing heavy lymphocytic and plasma-cell infiltration. This was first diagnosed as tertiary syphilis. *A*, reduced 25% from mag. × 97. *B*, reduced 25% from mag. × 194.

nally, associated with exudation. There was also marked edema of this area, extending into the neck. Biopsies of these areas on May 13, 1957, showed chronic inflammation, and the possibility of malignant lymphoma or anaplastic carcinoma was suggested on histologic section on June 5, 1957. At about this time, daily temperature elevations reoccurred (101-104 F), and despite an increase in steroid dosage and changing antibiotics, patient pursued a steady downhill course, with rapid progression in the size of the lesion causing difficulty in breathing and swallowing, with accompanying malnutrition and inanition.

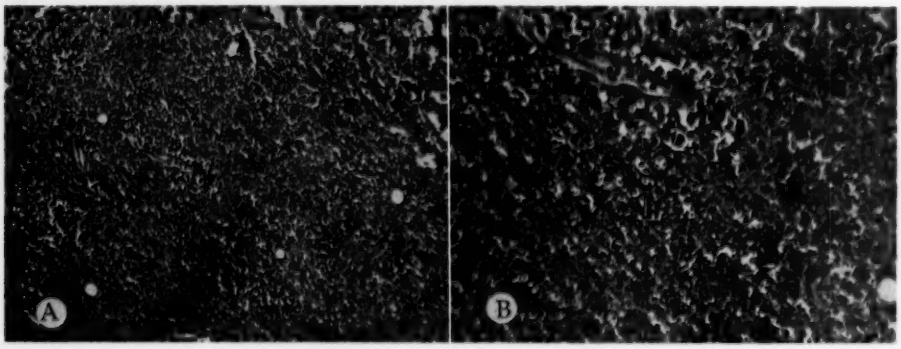
A tracheotomy was performed on June 18, 1957, with frequent aspirations necessary. However, the patient developed bronchopneumonia and died on June 24, 1957.

Pathologic Findings.—At autopsy (Fig. 4) there was marked induration and edema, with extensive inflammation involving the face, neck, anterior chest wall, mediastinum, trachea, and bronchi; pleuritis; areas of bronchopneumonia in lower lobes, and bilateral pleural effusion, all felt to be due to contiguous inflammatory spread from the primary process.

Microscopic examination of the ulcerated area of the face and sections of the cervical and anterior mediastinal lymph nodes revealed widespread areas of acute necrotizing inflammation, composed of neutrophils, lymphocytes, plasma cells, and mononuclear cells, which included histiocytes and epithelioid cells of a reticulum-cell type. A few of these latter cells were very similar to Reed-Sternberg cells. However, there was no evidence of granulomatous nodules of the type seen in Hodgkin's disease.

The remainder of the gross examination and microscopic sections of other tissues, including bone marrow, revealed no positive findings. A final diagnosis of lethal midline granuloma of the face was made in this case, with secondary involvement of contiguous structures leading to death.

Fig. 6.—Biopsy section from left side of face and nose four months after Figure 5, showing gangrenous necrosis and large mononuclear cells resembling lymphomatous cells. *A*, reduced 25% from mag. × 97. *B*, reduced 25% from mag. × 194.



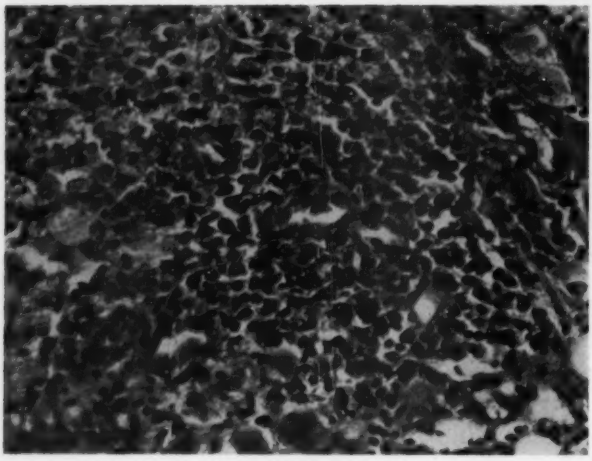


Fig. 7.—Biopsy section from left side of face and nose four months after Figure 6, showing pleomorphic infiltrate; × 246.

Comment

The etiology of this condition is unknown. Whenever a case is found, such entities as bacterial infection, syphilis, tuberculosis, Boeck's sarcoid, fungous disease (especially histoplasmosis), neoplastic disease, leprosy, mycosis fungoides, chronic tularemia, anthrax, and yaws, should be considered. All of these have been suggested at one time or another as etiologic possibilities. No etiologic agent, even after repeated cultures and animal inoculations, has been found, although some investigators have suggested Staphylococcus and/or Streptococcus, which are commonly found in the lesion. Control of the organisms by antibiotics, however, has usually failed to affect the course of the disease, and therefore they are felt to be merely contaminants. Several authors have suggested the disease to be on an allergic basis, i. e., a form of periarteritis nodosa, when, on biopsy, they demonstrated a necrotizing arteritis with eosinophils in a small group of cases, but the remainder of the findings were not compatible with this clinical entity.[3,4] Others have suspected a neoplastic etiology, with various forms of lymphoma and sarcoma being suggested.[5] Bergqvist and Koch [6] felt this to be a new tumor, not

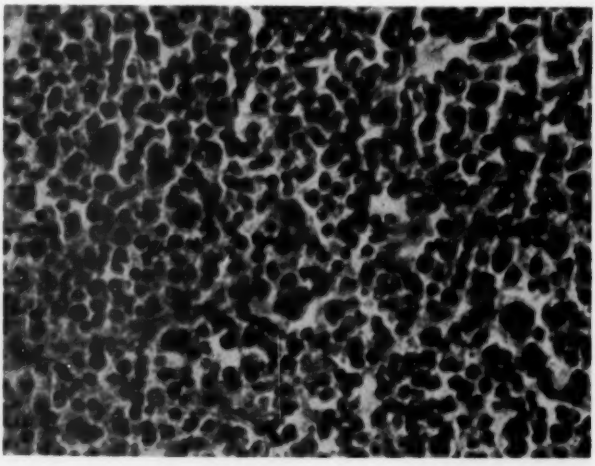


Fig. 8.—Autopsy section of cervical lymph node showing proliferation of atypical reticulum cells, some resembling Reed-Sternberg cells. Reaction confined primarily to the sinusoidal areas of the cervical and anterior mediastinal lymph nodes; × 424.

previously described, which was so affected by secondary inflammatory changes that the whole microscopic structure was distorted. In three cases reported by a group in Brazil[7] and one case by a group in England,[8] it was felt that the underlying etiology was reticulum-cell sarcoma. This diagnosis was based on large biopsy specimens from the facial lesion and suggestive findings seen on microscopic study of sections of liver and spleen.

Lethal midline granuloma of the face has a highly characteristic clinical course in most patients, characterized by progressive destructive mortification of tissues of the face with ulceration and necrosis, leading to eventual death within a period of several months. The cause of death is usually terminal meningitis, brain abscess, septicemia, or pulmonary complications, with accompanying inanition. Since this course is very similar to the one which we have already described in presenting this case and also to the one found in Stewart's classical description of the disease,[9] I will not expound on it any further. Since 1941, there have been a few instances of reported recovery,[10] but unfortunately these cases were atypical in their clinical course or the follow-up period was too short to classify them as cures, since temporary remissions do occur in this disease, as has been shown in the case presented in this article.

Laboratory diagnosis is essentially one of exclusion, with positive laboratory tests being conspicuous by their absence. It must be suspected in patients who develop a chronic progressive and destructive ulcer of the midline facial structures which fails to respond to local therapy, antibiotics, and chemotherapy. Failure to find a specific etiologic agent by culture, animal inoculations, serologic studies, or agglutination tests leads to biopsy, which reveals a coagulation type of necrosis with or without formation of granulomas. In most instances, the tissue is composed of numerous inflammatory cells in a predominantly loose stroma, which may resemble granulation tissue. Cells are mainly lymphocytes, plasma cells, and histiocytes. Eosinophils, neutrophils, multinucleated giant cells, and reticulum cells are sometimes seen. Special stains for tuberculosis bacilli and Mycobacterium leprae, fungi, and yeast are negative.

The disease has proven to be essentially a local entity, involving the face and contiguous structures terminally, with infrequent reports of dissemination of the disease being more misleading than helpful in arriving at a diagnosis. The typical case does not have widespread lesions, although one case with systemic lesions was described recently by Spear and Walker.[11] An interesting sidelight, which seems to be somewhat prevalent throughout the literature, is the varied specific diagnoses given this lesion on early biopsies, as also occurred in this case, before and during hospitalization, prior to final diagnosis. Syphilis, carcinoma, and, especially, various types of lymphoma are the main offenders.

Among the earlier forms of treatment, which were totally unsatisfactory, were local therapy and parenteral drugs, including heavy metals. Various antibiotics have been used with only temporary early response, by eliminating secondary invading organisms. Radium and roentgen therapy (small doses of 100 r given one to two times a week for 6-10 weeks) have produced, in a few instances, temporary healing of the ulcers.[12-14] Corticotropin (ACTH) and cortisone have given some encouraging results, with an occasional reported recovery,[10] but usually there has been only temporary arrest, with recurrences when the steroids were stopped. In 10 cases studied in Sweden by Hultberg et al., it was found that a combination of irradiation and adequate cortisone therapy yielded better results, with good control and even complete healing of the lesion in one case. However, the other cases, after temporary improvement, became refractory to cortisone, even with large doses. Others have reported cases to progress more rapidly with steroid therapy.

In this present case, wide surgical debridement with subsequent grafting, even though done late in the course of the disease, brought about a complete arrest in growth with marked healing of the lesion for about two months, following which there was recurrence, with then a progressive downhill course to death.

Conclusions

In conjunction with the case herein presented and a careful survey of the literature, several interesting clinical features have been found to be present in this rare entity, which include (1) nasal congestion preceding the lesion by several months and frequent occurrence of sinusitis during the course; (2) constant location of the original lesion in vicinity of the nasal septum; (3) no regional lymphadenopathy; (4) despite marked local involvement with high temperatures at times, usually a normal WBC and differential count; (5) patient feeling relatively well, with little in way of systemic symptoms up until the very latest stages of the disease, and (6) temporary remissions in growth of the lesion, frequently seen, possibly spontaneously occurring or as a result of therapy.

Diagnosis is made by the characteristic clinical picture, by excluding other specific entities through extensive laboratory testing, by the rather nonspecific histological findings, and by the remorseless progression, refractory to all therapy.

Constant and unaccountable is the complete lack of effective resistance to this lesion by the defensive mechanism of the body.[2]

If any present-day treatment is to offer any hope, it should be carried out as early as possible in the course of this disease and should include wide surgical debridement in conjunction with and followed by massive antibiotic and steroid therapy.

Summary

A case of lethal midline granuloma of the face is presented, with a brief review of the literature on the subject, stressing the difficulties in its diagnosis and the shortcomings in its treatment.

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The Marfan Syndrome

Report of One Case with Autopsy, Special Histological Study, and Review of the Literature

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The Marfan syndrome, or arachnodactyly, is a relatively rare familial disorder of unknown etiology characterized by widespread abnormalities of the skeletal, cardiovascular, and ocular systems in which a generalized elastic tissue disorder has often been suggested as the primary fault in pathogenesis.[1,2]

It will become apparent below that the cardiac lesions of the Marfan syndrome may involve any valve or portion of the heart and aorta, as well as the direct branches of the latter. This syndrome is unusual, but its importance has increased with the era of cardiovascular surgery.[1-3] In 1896, Marfan,[4] in reporting the first case, described disproportionately long extremities and long spidery fingers. Achard,[5] coined the term "arachnodactyly," but the eponym, preferred by some,[1] has continued to be used. General abnormalities, including arachnodactyly, relaxation of joints, lack of muscle tone, scant subcutaneous panniculus, dolichocephaly, high arched palate, large misshapen ears, pigeon breast, kyphoscoliosis, pectus excavatum, and pes planus, as well as occasional webbing of the fingers and toes, are features of the complete syndrome.[1,6] Ocular abnormalities may include ectopia lentis, abnormally small lens, redundant or broken suspensory ligament, and small poorly reactive pupils.[1,7] Profound alterations in cardiovascular structure and consequently in hemodynamics, especially aortic and mitral regurgitation; aneurysmal dilatation of the aorta; dissecting aneurysm of the aorta, and dilatation of the pulmonary artery are often seen.[8,9] A few of the patients have also shown significant or probably significant congenital structural defects of the heart or great vessels [13,14,36].

Fig. 1.—Hands illustrating arachnodactyly.

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McKusick preferred the designation, "the Marfan Syndrome," since Marfan described only skeletal abnormalities, while the syndrome encompasses cardiovascular and eye involvement described later by others (personal communication).

The study reported herein was done during a tenure as Instructor in Internal Medicine and Fellow in Pathology, University of Virginia Department of Medicine, Charlottesville, Va. Present address: 312 S. Washington St., Alexandria, Va.

The following people helped in reviewing tissue sections or editing the manuscript: Dr. Edward P. Cawley, Professor of Dermatology and Syphilogy; Dr. James E. Kindred, Professor of Anatomy; Dr. William Parson, Professor of Internal Medicine, and Dr. David E. Smith, Professor of Pathology, University of Virginia Department of Medicine; Dr. Victor A. McKusick, Associate Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore.

Fig. 2.—Gross photograph of heart, showing hypertrophy of myocardium, endocardial and valvular changes, dilatation of the aortic ring, rolling of valve margins and widening of commissures, dilatation of ascending aorta, and elevation of coronary ostia.

[39,52] (7 cases of 68). Changes of the right side of the heart have been described somewhat less frequently and seem less important hemodynamically than changes of the valves and endocardium on the left.[9,25,45,61] The characteristic microscopic lesion of the aorta, consisting of cystic degeneration of the media and fragmentation of the elastic strands, was adequately described in 1943.[10]

It is estimated [1,2] that over 350 cases of Marfan's syndrome have been reported in the literature. Reports of autopsied cases are, however, relatively few, numbering about 73.[1,3,8,9,11-54,61,62] Five of these were in children under 2½ years of age with no microscopic studies reported or no microscopic evidence of the disease in the cardiovascular system.[11,12,16,18,21] Two children

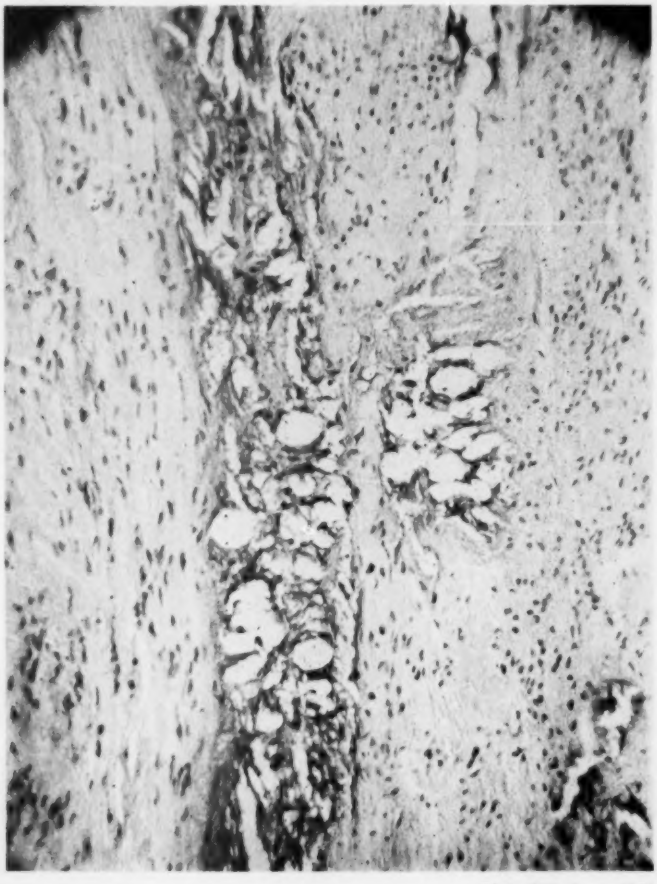

Fig. 3.—Photomicrograph of the ascending aorta, showing cystic medial necrosis. Hematoxylin and eosin; reduced approximately 15% from mag. × 225.

aged 10 months showed mild but typical aortic lesions microscopically.[9,45] Of the remaining 66 cases, 49 [1,3,8-10,13,19,20,23-54,61,62] had at least minimal microscopic studies reported.

It is apparent on reviewing the literature that the description of this condition is not yet entirely complete even for the cardiovascular system, as unusually widespread vascular changes were encountered in the presently reported case. Microscopic studies of many tissues, particularly periarticular and ligamentous, are few or nonexistent. The one significant exception is a microscopic study of periarticular structures about the knee in one case.[45] In view of the postulated elastic tissue defect [1,10] and the animal studies,[55,59] in which feeding sweet pea (Lathyrus odoratus) seeds or meal has been found to produce both skeletal and cardiovascular abnormalities in some respects similar to those found in the Marfan syndrome, it seems likely that if this theory is correct, it should be possible to demonstrate pathological changes in elastic tissues outside the cardiovascular system in humans. Lumbar intervertebral disk with surrounding ligamentous structures, lungs, trachea, and skin in this case were studied microscopically with special stains in the hope of making more information in the human available for comparison. It is fur-

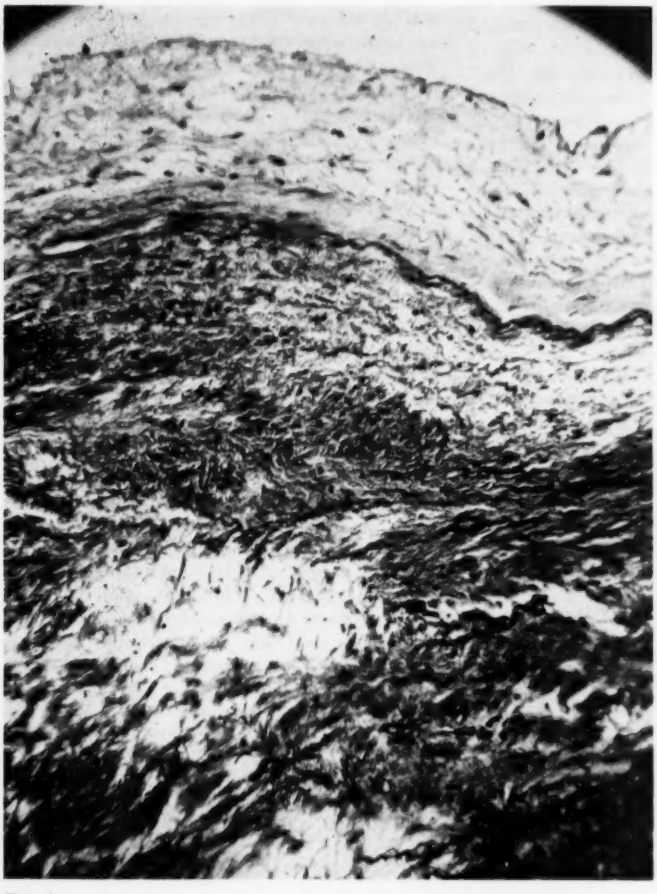

Fig. 4. — Photomicrograph of intima and media with elastic tissue stain, revealing fragmentation of the internal elastic membrane and other elastic strands. Cystic medial necrosis is also seen. Verhoeff-Van Gieson; reduced approximately 15% from mag. × 225.

ther the purpose of this report to review the cardiovascular abnormalities occurring in the Marfan snydrome.

Report of Case

The patient, a 28-year-old draftsman, was first seen as an outpatient at the University of Virginia Hospital on July 12, 1955, for consideration of insertion of a plastic valve in the aorta. No pertinent family history could be obtained. As far as could be ascertained, his development, except that he was considerably taller than the other members of his family, had been entirely normal until the age of 15 years, when he first became aware that the left side of his chest was more prominent than the right. For five years he had worn glasses because of severe myopia. Past history was otherwise not contributory. Two years before being seen he had noted mild but gradually progressive exertional dyspnea. For two weeks he had complained of severe dyspnea, palpitations, and a cough, which had had their onset during a long automobile trip.

Physical examination revealed him to be a tall thin poorly developed white man with little subcutaneous fatty panniculus, a high arched palate, extremely long fingers, and a ridge of the left hemithorax at the costochondral junction. He wore thick glasses and appeared much older than his stated age. Blood pressure was 150/60-0. Peripheral signs of aortic insufficiency were present. The lungs were clear to percussion and auscultation. The heart was greatly enlarged to the left. The apical impulse was diffuse. An aortic pulsation could be felt in the suprasternal notch. The aortic second sound was low in intensity. Systolic and diastolic murmurs were heard over the entire precordium, but they were of greatest intensity in the aortic and apical regions. The liver edge was palpable but did not pulsate. There was no venous distention, cyanosis, edema, or ascites.

The electrocardiogram showed left axis deviation, prolongation of the QRS interval, and T-wave changes, compatible with left ventricular hypertrophy and strain. On fluoroscopy the heart showed moderate general enlargement with pronounced enlargement of the left ventricle.

He was sent home on a regimen of mildly restricted activity. Shortly thereafter he developed signs and symptoms of progressive congestive heart failure and angina pectoris, for which he was digitalized by his local physician in late July, 1955. The initial response was good, but later symptoms were progressive in spite of salt restriction and diuretics.

On Oct. 22, 1955, he was admitted to this hospital. Physical findings were unchanged from those in July, with the exception of signs of severe congestive heart failure, with a 20 lb. weight increase and a mild acute pharyngitis. The optic lenses were normal in appearance and location, but the pupils reacted poorly. Little response was noted to the medical regimen, consisting of antibiotics, diuretics, digitalis, salt restriction, and bed rest. Laboratory studies, including complete blood cell count, serologic tests for syphilis, urinalysis, and serum electrolytes, were normal. An electrocardiogram was unchanged from his previous tracing. Ten days after admission, while sitting on the side of his bed, he fell forward, and he was dead when examined by a physician a few seconds later. Final clinical diagnosis was chronic valvular rheumatic heart disease with aortic regurgitation, or the Marfan syndrome.

Examination of the patient's 2½-year-old daughter revealed a scant fatty panniculus, high arched palate, mild thoracic scoliosis, and long fingers and toes, as well as hyperextensibility of joints. Cephalic measurements, eyes, and cardiac evaluation were normal. She was underweight and tall for her age.* Other members of the family would not submit to interview or examination.

Autopsy.—The body weighed 162 lb. and was 6 ft. 11 in. in length. There was poor muscular development, little subcutaneous panniculus, long slender fingers and toes, moderate thoracic scoliosis (concavity to the right), prominence of the left side of the chest due to buckling forward at the costochondral junctions, dolichocephaly, large misshapen ears, a high arched palate, distention of neck veins, and 4+ edema of the lower extremities and presacral region. Considerable fluid was present in the abdominal and thoracic cavities.

The heart weighed 745 gm. All chambers, but particularly the left ventricle, were hypertrophied and dilated. A patch of chronic adhesive pericarditis was present on the posterior epicardial surface of the left ventricle. The tricuspid, pulmonic, mitral, and aortic valves measured 14.5 cm., 9.1 cm., 14.0 cm., and 10.5 cm. in circumference, respectively. The pulmonic and tricuspid valve cusps were normal in appearance. The pulmonic artery showed a striking outpouching behind its valve cusps, and its intima was wrinkled. The mitral and aortic valve cusps were thickened, and the edges of the latter were rolled outward, but the aortic commissures were not widened. The acoronary aortic cusp was 6 cm. in length, and it spanned a large corresponding aneurysmal dilatation at the base of the aorta. The other aortic valve cusps were shorter. The sinuses of Valsalva were dilated, and the ostia

* She fell into the 98th percentile for height and into the 50th percentile for weight (Harold C. Stewart and Assoc. Charts, Dept. of Maternal and Child Health, Harvard School of Public Health, Boston).

of the coronary arteries were situated 2.5 cm. above the aortic ring. On the endocardium of the left atrium above the posterior leaf of the mitral valve were several grayish-yellow plaques. The left ventricular endocardium over the interventricular septum was thickened and opaque. The aortic dilatation extended to involve the arch, which showed fusiform aneurysmal widening. On the posterior surface of the ascending aorta was a 4 cm. patch of thickening; elsewhere the intima of this part of the aorta was wrinkled. In the transverse and descending aorta the intima was normal in appearance except for a few atherosclerotic plaques. In the abdominal aorta, and the splenic, renal, mesenteric, common iliac, and internal iliac arteries as far as they could be opened there were patches of puckering and scarring of the intima which, as in the ascending aorta, grossly resembled syphilitic change.

The remainder of the organs showed no pathological changes of note aside from those of moderate chronic passive congestion and a rather marked degree of diffuse pulmonary emphysema. The brain was normal in appearance.

Microscopic Examination. — The myocardium showed evidence of hypertrophy. Thin blue-staining strands of material forming a reticular pattern were present in the myocardial interstitial spaces but particularly in the subendocardial region, valves, and perivascular regions. The ends of the strands were frayed and fragmented. The strands stained black with Weigert's and with Verhoeff-Van Gieson's stains and chromotropically with toluidine blue. This change was most abundant in and about the base of the aortic and mitral valves. Small cystic areas containing a blue coagulum, which showed an intense chromotropic reaction with toluidine blue, were seen in areas where the previously described strands were most abundant. No evidence of rheumatic fever could be seen. A few tiny areas of cystic degeneration were present in the media of the coronary arteries. The internal elastic lamina of the coronary arteries was not disturbed. In the transverse thoracic aorta the intima was thickened at some points by collections of yellow material resembling lipoids. These plaque-like patches of intimal thickening did not stain with Sudan IV. Instead, these plaques showed an intense chromatropic reaction with toluidine blue which was absent in the Sudan-positive atherosclerotic plaques found in the abdominal aorta. In many areas, the internal elastic membrane was fragmented and the ends of the fragments were frayed into many small strands. These small fragments stained blue with hematoxylin and eosin, black with Weigert's and Verhoeff-Van Gieson's stain, and metachromatically with toluidine blue. In other areas the internal elastic membrane had completely lost its identity.

In the aortic media there was increased vascularization, disarrangement of orientation, and fraying of elastic fibers. There were large areas of cystic degeneration of a much greater number and size than in the heart valves but with identical staining characteristics. All these changes were most marked in the ascending aorta but were also present in the remainder of the vessel. A few small deposits of Sudan IV-positive material were present in the media, usually closely associated with vasa vasorium. The splenic artery (mid portion) and iliac arteries showed changes similar in kind and degree to those in the abdominal aorta. The innominate artery, right subclavian artery, right common carotid artery, and mesenteric artery, with many of its unnamed branches, showed fewer cystic changes and milder but significant changes in the elastic lamellae. The left subclavian artery, left common carotid artery, and the renal arteries at their origin and within the renal pelvis showed minimal metachromatic reactions and changes in elastic fibers which were considered abnormal only because of the patient's age. The intracranial internal carotid arteries, cerebral arteries, inferior vena cava, and common iliac veins showed no pathological changes. The main pulmonary artery and its primary branches showed abundant interstitial blue-staining coagulum which was positive with toluidine blue. Elastic tissue stains indicated only minimal fragmentation of elastic fibers in the pulmonary artery. In a few places the internal elastic membrane showed changes identical to those described in the aorta. A few toluidine blue-positive Sudan-negative intimal plaques were present in the pulmonary artery. No useful information could be gained from periodic acid-Schiff- and phosphotungstic acid-hematoxylin-stained sections of the heart and vessels in that consistent additional changes in the previously described lesion were not demonstrated.

Sections of the trachea near its bifurcation failed to show any disorder of the longitudinally arranged elastic fibers in the submucosa, and no metachromatic changes were present. The lung itself showed moderate emphysema, mild chronic passive congestion, and occasional fresh and organizing thrombi in small vessels. The intrapulmonary vessels failed to show abnormality of elastic tissue or metachromatic changes with appropriate stains. Elastic tissue within alveolar walls was within normal limits. The liver showed severe chronic passive congestion and a distinct fibrosis about central veins. The kidneys showed only mild chronic passive congestion, as did the remainder of the viscera. The skin was normal with routine stain and as to amount and appearance of elastic tissue in the dermis with special stains. The anterior spinous ligament from the lumbar region showed no recognizable metachromatic changes. Only a few elastic strands located between the ligament

and the lamina fibrosa were stainable in the sections. Those elastic tissue strands present were not frayed or fragmented, as was the case in the heart and aorta. A distinct herringbone pattern was present in some areas of the intervertebral disk.

The pituitary, brain, bone marrow, and cortical bone showed no pathological change.

Final Anatomic Diagnoses.—Arachnodactylia; chromotropic and cystic degeneration of the aorta and pulmonary, pancreatic, and iliac arteries; dilatation of the aortic ring, ascending aorta, and sinuses of Valsalva of the aorta and pulmonary artery; edema of the lower extremities; ascites; hydrothorax; hydropericardium; chronic passive congestion of the liver; congestion of the lungs and kidneys; generalized emphysema of the lungs.

Comment

The diagnosis of the Marfan syndrome in the case was considered established by the characteristic physical abnormalities and classical though unusually widespread cardiovascular abnormalities at autopsy. According to McKusick,[1] in less than 15% of cases will a family association be absent if this is strenuously sought. It is also emphasized that classical ocular abnormalities may occasionally be absent. Skeletal abnormalities, the best initial hint of the diagnosis, may be minimal in families where most members are pyknic in stature unless the person in question is compared with his own family group rather than the general population,[1,9] thus in part accounting for the forme fruste. This fact should be kept in mind when evaluating patients for aortic valve surgery, since at least theoretically[2] and in the two cases[3,53] where a Hufnagel valve has been inserted it has been of very temporary or no value. A high index of suspicion, careful fluoroscopy, and, in doubtful cases where surgery is contemplated, angiocardiography, will probably serve to avoid unnecessary and dangerous surgery, even in cases where classical skeletal and ocular abnormalities or family history are absent.

The previously described abnormalities of cardiovascular, ocular, and skeletal abnormalities have been enumerated in the introduction. In most cases, when dilatation of the aorta is present it ends abruptly at the innominate artery,[9] but dilatation of the abdominal aorta has been described.[39,40] Diffuse microscopic changes of the aorta beyond its arch have also been reported previously.[19,25,36,38-40,50,54] The circumference of the abdominal aorta was not altered in this patient, but gross changes in the intima and media were apparent in the aorta below the diaphragm. Microscopic changes were present in the descending thoracic aorta and were only slightly less pronounced in the abdominal aorta than in the ascending aorta. Gross wrinkling and scarring of the intima and scarring of the media in the splenic and iliac arteries have not been mentioned before. Minimal microscopic changes close to the origins of some of the larger arteries arising from the aorta have been described,[36,45,48] and significant cystic changes involving the carotids associated with dissecting aneurysms of both carotids have recently been reported.[54] In only the latter case was the degree or extent of the changes similar to those seen in this case. Changes in the pulmonary artery and its major branches, including dilatation and microscopic changes ranging from minimal to severe, have been repeatedly seen.[9,14,19,31,36,39,42] The presence of dilatation, small interstitial deposits of metachromatic coagulum, and mild changes in elastic lamellae without cyst formation, smooth muscle disorientation, or hypervascularization of the media, in the pulmonary artery and less severely affected areas of the aorta, carotids, and subclavian arteries, may lend support to the view of Gore[60] that the "degeneration" of elastic lamellae is a primary event in the sequence of changes leading to thickening, weakening, and dilatation of vascular walls, with eventual rupture or dissecting aneurysm, which are so commonly the terminal event in the Marfan syndrome. Twenty-five[1,3,8,9,20,22,24,25,28,29,35,40,41,44,47,50,53,54] of the 73 reported autopsied cases have had dissecting aneurysm or rupture of the aorta. Trauma to the chest, events greatly increasing the intrathoracic pressure, or

pregnancy [1,3,9,53] seem frequently to initiate either cardiac decompensation or aortic dissection, and the history of such an association may be helpful in clinical diagnosis. Elevation of the coronary ostia above their usual site and dilatation of the aortic ring, giving rise to coronary insufficiency and aortic regurgitation, followed by hypertrophy and dilatation of the heart, particularly the left ventricle, with rapidly progressive congestive heart failure, are well-known features of the condition [1,8,9,15,19,20,23-25,30,33,35-37,39,41-43,45,48-50,51-53] and were present in this patient (and 36 of the previously autopsied cases). Gross thickening, asymmetry, and elongation of cusps, particularly of the aortic valve, as seen here are common. These changes are often associated with microscopic fibrotic thickening, elastic strand fragmentation, and patchy metachromasia [1,3,9,15,17,19,20,24-26,28,30,33,36,39,40,43,45,49-53,54] and underlie gross changes contributing to disordered hemodynamics. McKusick [1,9] refers to the frequent occurrence of varicose veins in persons with the Marfan syndrome. The patient herein reported showed no clinical evidence of varicosities. Special stains of the lower inferior vena cava and common iliac veins failed to reveal any metachromasia or disordered elastic fibers. No veins from the lower extremities were studied microscopically.

In an attempt to find other areas where elastic tissue disorder might be demonstrated, skin, trachea, and lung sections were studied with special stains. No chromotropic reaction was elicited with toluidine blue, and elastic tissue stains showed normal amounts and continuity of this tissue. It should be noted that pulmonary cystic disease has previously been mentioned.[1] Pulmonary emphysema was found in this patient in the absence of any of the usual etiologic factors being identifiable clinically, and so in this case it could conceivably be causally associated with the basic disorder of the Marfan syndrome.

Gross abnormalities of the spine and intervertebral disk are not unusual clinical findings.[1,6] These changes have also been attributed to the elastic tissue defect. Microscopic studies of these structures in this condition were not located in the present review of the literature. In the present patient, there was no fragmentation or fraying of the few elastic strands present between the anterior spinous ligament and the lamina fibrosa of lumbar intervertebral disks. Elastic fibers were absent in the intervertebral disks. No chromotropic reaction with toluidine blue was present in the intervertebral disks or anterior spinous ligaments. With routine stain, all sections of the lamina fibrosa showed many areas with a distinct "herringbone pattern" which was absent in three controls and present in two others. Whether the presence of this pattern represents a pathological change, a normal change of aging, or is an artifact produced by minor variations in handling some sections is not known. It is known [63] that the connective tissue in the lamina fibrosa is arranged in what might be described as a herringbone pattern, with main fibers giving rise to many secondary thinner fibers which extend out from the main strand in an oblique fashion roughly parallel to each other. Certainly the ligamentum nuchae should be the ideal tissue to study in this regard, although the elastic fibers in this structure are not as numerous in man as in some lower animals.[63,64] Unfortunately this structure could not be studied.

McKusick,[65] in an editorial, has reviewed the evidence and the various theories so far advanced to explain the various phenic manifestations of genetically determined disorders. The failure to demonstrate microscopic changes outside the cardiovascular system here, in spite of the fact that undeniable phenic manifestations were present, may be explained by the relative crudeness of the methods used, sparsity of elastic fibers in the various structures examined, and differences in types and degree of stress to which these structures are subjected but is perfectly compatible with the concept [65] that the basic defect may reside not in the

elastic tissue itself, as it is ordinarily understood, but in some tissue element common to elastic tissues and other supporting structure elements outside the cardiovascular system. This fault common to many connective tissue components has so far defied demonstration.

It is felt that important information, whether negative or positive, is still to be gained from histologic study of tissues, particularly in those outside the eye and cardiovascular system, and that those studies may add to our knowledge of the etiology and pathogenesis of the Marfan syndrome.

Summary and Conclusion

The literature in cases of arachnodactyly where postmortem studies were reported is reviewed, and our present clinical concept of the condition, stated, with particular reference to the widespread involvement of the cardiovascular system. A case of arachnodactyly with unusually widespread cardiovascular abnormalities in which special studies of tissue not ordinarily studied in detail were made was described. The frequency of dissecting aneurysm and aortic insufficiency, as well as the necessity and means of differentiating arachnodactyly or its forme fruste from acquired or congenital aortic valvular disease, are reviewed. The importance of making this differentiation is discussed. The theory of an inborn generalized defect in elastic connective tissue is mentioned and the point implied that, at least microscopically, with the methods employed, demonstration of this proposed defect outside the cardiovascular system has not been successful. It is concluded that the defect is probably not limited to elastic tissue but is most likely due to abnormality of some substance common to elastic tissues and supporting structures outside the cardiovascular system, which abnormality was not recognized by the methods used here.

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Staphylococcal Bacteremia and Osteomyelitis Successfully Treated with Novobiocin

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Novobiocin (Cathomycin), derived from the actinomycete Streptomyces spheroides, has now been added to the growing list of antibiotics useful in clinical medicine. Recent studies [1-8] have shown this drug to be effective in infections due to many Gram-positive and a few Gram-negative organisms, and there has been particular interest in the demonstration that novobiocin is active against many strains of Staphylococcus.

The following case report illustrates the effectiveness of novobiocin used in the treatment of a patient with staphylococcal bacteremia and focal areas of osteomyelitis. In addition, the case is of interest because, while under treatment, the patient developed a reaction to the novobiocin, which subsided spontaneously despite the continued use of the drug.

Report of Case

The patient, a 58-year-old white man, was admitted to the Medical Service of the McKinney Veterans' Administration Hospital for the fourth time on Dec. 31, 1955, complaining chiefly of intermittent feverishness, chilly sensations, productive cough, and bilateral chest pain of two weeks' duration. He dated the onset of his illness to Dec. 17, 1955, when he first noted a "sticking" pain in his left lower anterior chest. On the following day he developed a recurrent cough, which from its onset was productive; the expectorated material was initially white, but subsequently the sputum contained purulent material and, on a few occasions, blood streaks. Two days after the onset of these symptoms, he experienced a series of generalized, shaking, teeth-chattering chills, associated with feverishness and followed by profuse perspiration.

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With the onset and progression of these symptoms, the patient sought the aid of his private physician and was given four intramuscular injections, presumably penicillin, and then received a course of "yellow capsules," which he continued to take until the time of his hospital admission. These capsules afforded him some slight improvement initially, but during the last few days prior to his admission he had noted some exacerbation of these complaints.

The patient had been followed intermittently at this hospital since 1950 because of the presence of a nodular pulmonary density, 1 cm. in diameter, incidentally found on a chest x-ray at the level of the right second anterior intercostal space. Sputum smears and cultures on several occasions had been negative for acid-fast bacilli, and serial x-rays had shown no essential change in the appearance of the lesion. Of additional significance in his past history is the patient's statement that he had spent several years during the 1920's in the San Joaquin Valley region of California and while there had been hospitalized with "valley fever." In recent years, he had lived in the eastern part of Texas, and he stated that he hunted frequently, shooting rabbits and squirrels. Although he did not handle or eat the rabbits, he had eaten squirrel meat on several occasions. He also recalled numerous tick bites he had received while hunting.

Admission physical examination revealed a well-developed and well-nourished white man who was moderately acutely ill, complaining of pleuritic left anterior chest pain. His temperature was 102 F orally; pulse rate, 104 and regular; respirations, 24, and blood pressure, 114/70. Several small discrete papulopustular lesions were present on the skin of the trunk, abdomen, and extremities, a few of which showed superficial scabs and crusting. The lung fields were resonant; fine inspiratory rales were heard at both bases, and these were more marked at the right base, where they extended from the posterior aspect laterally into the right axilla.

The white blood cell count at the time of admission was 12,250, with a differential count showing 75% neutrophiles, 17% lymphocytes, and 8% monocytes. The sedimentation rate was 35 mm. in one hour. Urinalysis revealed 2 to 3 white blood

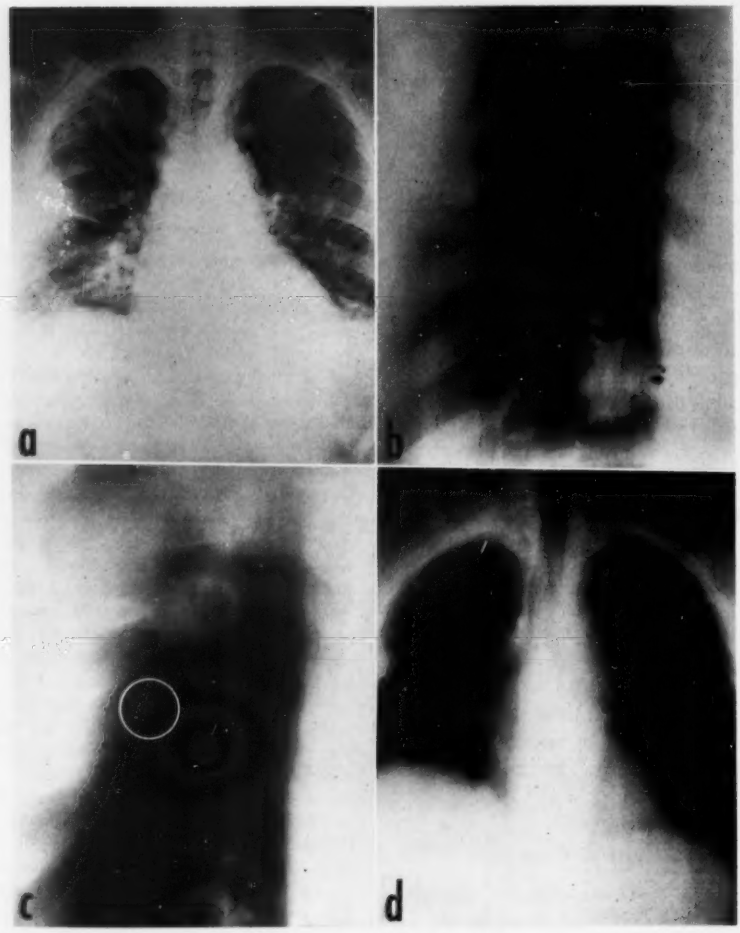

Fig. 1.—*A*, admission chest x-ray showing diffuse bilateral pneumonia. *B*, anteroposterior planigram at 4 cm. level, done five days after admission, showing large nodular density at right base. *C*, anteroposterior planigram at 7 cm. level, same date. Large nodular density in right upper lung field, within which is an irregular area of radiolucency, interpreted as cavitation. Circle outlines the smaller nodular lesion, which had been present and unchanged on patient's chest films dating to 1950. *D*, anteroposterior planigram at 11 cm. level, same date. Nodular density in right midlung field, bordering on transverse fissure.

cells and a rare white blood cell clump per high-power field. The blood urea nitrogen was 11 mg. %, and the fasting blood sugar, 87 mg. %. Tularemia agglutinations were negative. Culture of a sputum specimen obtained at the time of admission subsequently yielded a light growth of Staphylococcus aureus, sensitive to penicillin, erythromycin, and chloramphenicol but resistant to tetracycline. Ten days later a repeat sputum culture yielded a moderate growth of the same organism with identical sensitivities.

After the admission laboratory studies and chest x-ray (Fig. 1*a*) had been obtained, a course of intramuscular penicillin was begun. However, after the first injection of that drug, he developed a generalized pruritic urticarial eruption. The urticaria subsided promptly with diphenhydramine (Benadryl), and the patient was switched to tetracycline capsules. Over the next few days, there was slight decline of his temperature into the low-grade range, from 99 to 100.4 F; however, during the second hospital week his temperature rose slightly to peaks of 100.6 and 101 F, and on Jan. 11, 1956, it reached 103 F. This rise in fever was associated with some increase in his left chest pain and cough, and, in addition, the patient developed pain,

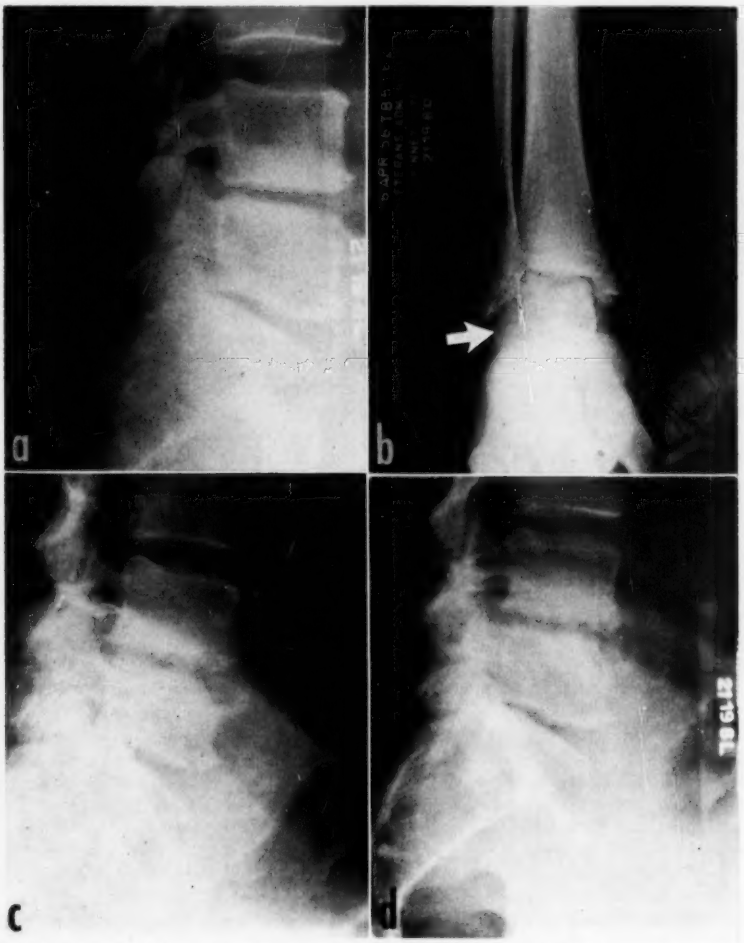

Fig. 2.—*A*, lateral view of lumbar vertebrae taken in January, 1956. *B*, anteroposterior view of right ankle, April, 1956. Arrow points to focal area of disruption of cortex of right talus. *C*, lateral x-ray of lumbar vertebrae, April, 1956, showing destruction of the opposing borders of the fourth and fifth lumbar vertebrae. *D*, lateral view of lumbar vertebrae, July, 1956, showing early callus bridging the interspace between L4 and L5.

associated with marked photophobia and injection of the bulbar conjunctiva, in the left eye. The eye consultant believed that the patient had developed an acute posterior uveitis, and a course of salicylates with scopolamine was instituted with instillations of a preparation containing hydrocortisone acetate and neomycin sulfate (Neocortef).

Planigrams of the chest done during the second hospital week (Figs. 1*b*, 1*c*, and 1*d*) revealed multiple pulmonary nodules, three in the right lung field and one at the left base. Within the nodular density on the left, and within two of the nodules in the right lung field, areas of radiolucency were seen which were interpreted as cavitation. The possibility that these might be metastatic tumor nodules was considered; an upper gastrointestinal series and an intravenous pyelogram were both normal. Skin tests gave positive reactions to tuberculin, coccidioidin, and histoplasmin. Complement-fixation and precipitin tests for coccidioidomycosis were negative. A blood culture drawn at this time revealed nine colonies of a coagulase-negative S. aureus, sensitive to penicillin, erythromycin, and chloramphenicol but resistant to tetracycline. Since the patient was apparently making a poor clinical response, the tetracycline was discontinued, and a course of erythromycin, 250 mg. every four hours, was begun. To enhance the effectiveness of

the erythromycin, he was also given a four week course of streptomycin, 1 gm. daily.

In the latter part of January, 1956, the patient showed gradual improvement, with concomitant clearing of the previous evidence of inflammation in the left eye. At that time he began to complain of pain in his lower back, and he stated that he had been told on several previous occasions that he had "arthritis of the spine." X-rays of the lumbar spine (Fig. 2*a*) revealed marked narrowing of the interspaces between L4 and L5 and between L5 and S1. He was seen in consultation by the orthopedic service, which believed that these changes represented those of osteoarthritis. A program of Buck's extension and intravenous mephenesin (Tolserol) was instituted and was carried out for a period of two weeks. This effected some subjective improvement, but the response was not dramatic.

The patient was continued on erythromycin therapy for a total of seven weeks, during which time his temperature subsided to normal, his serial chest x-rays showed progressive bilateral clearing, and he improved subjectively. Repeat chest planigrams on Feb. 28, 1956, no longer showed evidence of cavitation within the pulmonary nodules. Sputum cultures revealed no pathogens, and blood cultures were sterile. After the erythromycin was discontinued, on March 1, the patient remained afebrile and subjectively much improved until March 13, when he again developed low-grade fever, with almost daily temperature elevations to 99.6 F. Associated with this, he began to complain of soreness, stiffness, and swelling of his right ankle, and exquisite tenderness could be elicited on pressure just below and posterior to the right lateral malleolus. X-rays of the right ankle (Fig. 2*b*) showed a small focal area of destruction with disruption of the cortex on the lateral aspect of the right talus; this was interpreted as an area of osteomyelitis. In addition, the patient again complained of pain in his lower midback, and repeat x-rays of the lumbosacral area (Fig. 2*c*) now showed destruction of the anteroinferior portion of the body of the fourth lumbar vertebra and the anterosuperior portion of the body of the fifth lumbar vertebra. These changes were interpreted by the radiologist as also representing areas of osteomyelitis. An attempt was made to aspirate the right ankle joint; a small amount of serosanguineous material was obtained, which on culture yielded two colonies of S. aureus, coagulase-positive and sensitive to penicillin, erythromycin, and chloramphenicol, while resistant to tetracycline. At the same time, pyuria appeared and urine cultures were positive for S. aureus, coagulase-positive, with the same antibiotic sensitivities. The prostate gland was normal to palpation, but culture of the prostatic fluid yielded the same organism. It was felt, then, that the patient had experienced hematogenous dissemination of the staphylococci and that the erythromycin had been bacteriostatic only. The organism obtained from the urine and prostatic fluid cultures was found to be markedly sensitive to novobiocin (Table 1), and a course of that drug was instituted on April 10, 1956. A bactericidal test of the organism with novobiocin showed marked bactericidal activity at all concentrations tested (Table 2).

The drug was well tolerated for the first week. On April 17, however, the patient's temperature rose to 100.6 F, and during the next week he showed daily temperature elevations to 101 F or above, reaching a maximum of 102.8 F on April 22. Associated with this fever, the patient experienced chilly sensations on several occasions and developed a pinkish-red maculopapular eruption on the skin over the upper back, shoulders, chest, and

TABLE 1.—*In Vitro Antibiotic Sensitivities of Staphylococcus Isolated from Urine and Prostatic Fluid*

Antibiotic	Minimum Concentration * Inhibiting Growth, μg/Cc.
Tetracycline HCl	No inhibition
Chloramphenicol	5.0
Erythromycin	0.312
Streptomycin	No inhibition
Bacitracin	10.0
Penicillin	0.312
Neomycin	0.312
Novobiocin	1.25

* Agar plate dilution test was employed and read to complete inhibition after 18 hours' incubation at 37 C.

TABLE 2.—*Bactericidal Test*: Approximate Number of Colonies Counted*

Duration of Exposure, Hr.	Concentration of Novobiocin, μg/Ml.								
	25.6	12.8	6.4	3.2	1.6	0.8	0.4	0.2	0.1
24	0	131	190	367	622	666	1380	1020	2940
72	0	0	few clumped together	1	30	50	6	70	6

* Number of viable staphylococci after varying degrees of exposure to different concentrations of novobiocin.

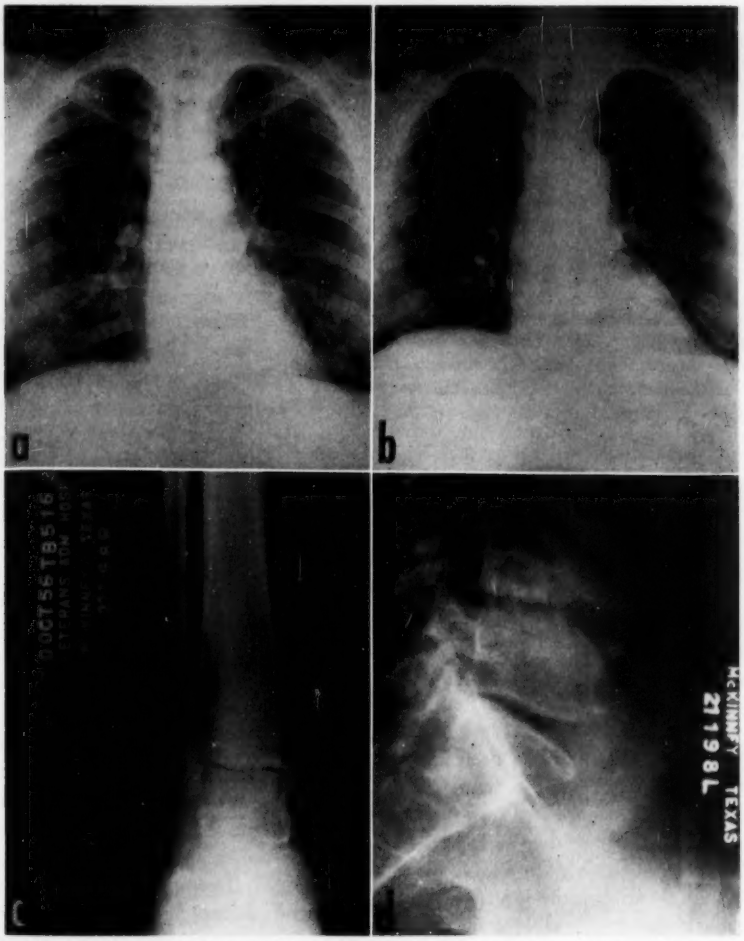

Fig. 3.—*A*, chest x-ray, July, 1956, revealing the marked bilateral resolution of the previous extensive pneumonia. *B*, chest x-ray, October, 1956, showing no essential change over the film of July. *C*, anteroposterior x-ray of the right ankle, October, 1956, showing evidence of complete healing of the previous area of osteomyelitis of the right talus. *D*, lateral x-ray of lumbar vertebrae, October, 1956, showing further bone deposition in the L4-L5 interspace.

upper abdomen, which subsequently appeared on the face and extremities. At the end of one week, despite the continued administration of novobiocin in constant doses (500 mg. every six hours), the constitutional reaction abruptly subsided. On April 25 he was afebrile, and he remained essentially so thereafter. The skin rash progressively faded but remained as a faint blush until early June. The novobiocin was administered for a total of seven weeks. There was no eosinophilia and no significant change in the leukocyte count at any time during the administration of the novobiocin. Urine cultures on April 9 and April 10, the day on which the novobiocin therapy was started, had revealed heavy growths of staphylococci. A urine culture on April 16 yielded seven colonies of S. aureus; a urine culture on April 19 was sterile, and thereafter all urine cultures obtained were sterile. Serial chest x-rays continued to show progressive resolution of the bilateral pneumonia, until only fibrotic residuals could be seen. There was progressive clearing of the evidence of inflammation in the patient's left eye. Serial x-rays of the lumbar spine and right ankle in April, May, and July showed no further evidence of bone destruction, and in the July film (Fig. 2*d*) there was thought to be evidence of reossification in the L4-L5 area.

After novobiocin therapy was discontinued, the patient remained essentially afebrile and without complaints. He became progressively ambulatory, and at the time of his discharge, in July, 1956, he was entirely asymptomatic. The chest x-ray had returned to an appearance comparable to films taken in previous years (Fig. 3*a*). The patient returned to the hospital in October, 1956, for follow-up examination. At that time he continued to feel well and had gained approximately 5 lb. in weight. He had noted no pain or discomfort in either his back or right ankle. Chest x-ray at that time (Fig. 3*b*) showed no essential change from the film of three months previous. X-rays of the right ankle (Fig. 3*c*) showed almost complete healing of the previous area of cortical disruption. X-rays of the lumbar spine (Fig. 3*d*) revealed considerable bone deposition between the bodies of the fourth and fifth lumbar vertebrae.

Comment

Several authors [2-5,7,9,10] have documented the occurrence of untoward drug reactions when novobiocin is administered. The reported incidence of these reactions has varied from 6%[7] to 41.3%.[4] Of the adverse effects associated with the use of this antibiotic, the one most commonly noted has been allergic dermatitis, at times associated with fever. This dermatitis has been manifested as either an urticarial or a maculopapular rash which is generally pruritic. Welch et al.[11] estimated the incidence of dermatitis to be 8.9% in a large group of patients receiving novobiocin injections and reported by various authors. Morton et al.[9] reported one case in which the drug was continued despite the development of a pruritic urticarial rash. Other untoward reactions to novobiocin which have been reported include nausea, diarrhea, depression of the white blood cell count, mild eosinophilia, and elevation of the serum bilirubin. Although experimental studies [4] have shown the development of severe degenerative changes in the liver and kidneys following the administration of novobiocin intravenously, most clinical reports have shown no overt evidence of either hepatic or renal impairment.

The patient reported here was admitted to the hospital with a severe bilateral ulceronodular pneumonia, and shortly after admission staphylococci were isolated from his sputum and blood cultures. During a prolonged course of erythromycin and streptomycin, the pulmonary infection progressively cleared and the patient slowly improved. Two weeks after these antibiotics were discontinued, however, fever returned, and he developed x-ray evidence of destructive lesions of the fourth and fifth lumbar vertebrae and of the right talus; cultures of material aspirated from the region of the right ankle, as well as cultures of his urine and prostatic fluid, yielded S. aureus. In vitro studies of this organism showed it to be sensitive to novobiocin, since a concentration of that antibiotic of 1.25μg. per cubic centimeter was sufficient to inhibit the bacterial growth. Further evidence of the marked bactericidal activity of the novobiocin was obtained from the demonstration that bacterial growth was almost completely suppressed after 72 hours' exposure to the antibiotic, even when the novobiocin was diluted to a concentration of 0.1μg. per cubic centimeter.

One week after the institution of novobiocin therapy, the patient developed fever, nausea, vomiting, and a generalized maculopapular eruption; these symptoms were interpreted as manifestations of drug hypersensitivity. Despite continuation of the antibiotic therapy, however, the constitutional symptoms and rash progressively cleared, and the patient completed a 42-day course of novobiocin therapy, during which the urine became sterile and the destructive bone lesions were arrested.

Summary

A case of disseminated staphylococcal infection is reported, in which novobiocin therapy was used effectively. The case presents several interesting features: (1) the dramatic response to the drug, including the arrest and apparent reversal of destructive bone lesions; (2) the marked in vitro bactericidal effect of the antibiotic, and (3) the appearance of adverse reactions to the

drug, which cleared as the drug administration was continued, so that the patient was able to complete a 7-week course of novobiocin therapy.

526 N. Locust St.

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Repair of Ruptured Interventricular Septum Complicating Acute Myocardial Infarction

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Rupture of the interventricular septum following myocardial infarction is being reported with increasing frequency both in autopsy material and as an antemortem diagnosis.[1-5] While the prognosis is uniformly poor, extended survivals are frequent enough [6] to warrant the consideration of corrective surgery. In one reported case,[7] repair was accomplished through an open cardiotomy aided by a pump oxygenator. At the present time it would seem desirable, in these high-risk patients, to attempt repair by a surgical procedure which avoids the added time and risk of an artificial circulation. The perforations secondary to infarction usually occur in the apical portion of the septum, often adjacent to one of the free ventricular walls.[6,8] A fairly rapid repair of these defects thus seems feasible, avoiding the additional hazards of a pump oxygenator. The following case report describes such a surgical approach in a patient in whom rupture of the interventricular septum occurred as a complication of myocardial infarction.

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Report of Case

A 61-year-old white man, a cabinet maker, suddenly developed the clinical picture of an acute myocardial infarction. He was hospitalized, and the clinical impression was confirmed by serial electrocardiograms which indicated the presence

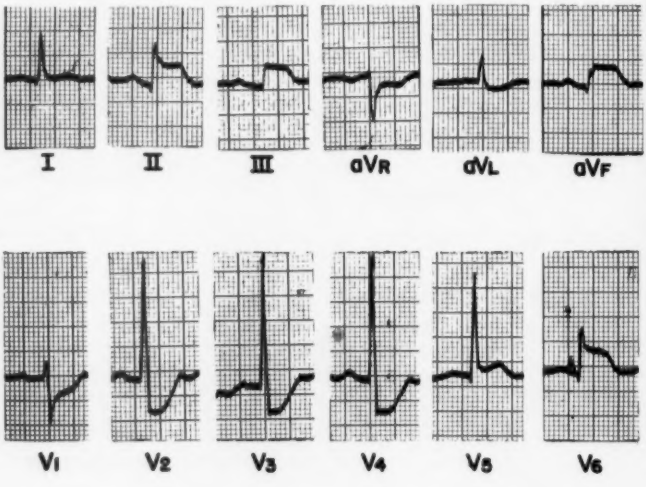

Fig. 1.—Electrocardiogram taken on the first hospital day, showing an extensive posterolateral infarction.

of a posterolateral infarct (Fig. 1) and serum glutamic oxalacetic transaminase activity, which was characteristically elevated.

While he was originally normotensive and not in failure, on the third hospital day he became dsypneic, diaphoretic, and hypotensive. Digitalis, quinidine, and levarterenol (*l*-norepinephrine) were administered. The patient had been receiving anticoagulants since admission. On the fifth hospital day he experienced chest pain not relieved by morphine, followed in a few hours by pulmonary edema, hypotension, and coma. A portable chest film taken at this time indicated the presence of a massive pulmonary infarct involving most of the right lower lobe. After emergency measures were instituted, the patient regained consciousness and slowly improved, but, despite the use of increasing concentrations of levarterenol (*l*-norepinephrine), the blood pressure could not be raised above 80/60 mm. Hg. He continued to receive digitalis, quinidine, and anticoagulants. On the 11th hospital day he was transferred to the Veterans Administration Hospital, where he was found to have mild pulmonary edema, cardiomegaly, and a Grade 3 rough holosystolic murmur, loudest at the third and fourth intercostal spaces along the left sternal border. It radiated as much to the right of the sternum as it did to the left and was associated with a systolic thrill over the same area.

The presence of a transient friction rub and an elevated white blood cell count at the time of admission to the Veterans Administration Hospital suggested extension of the myocardial infarction, and so the patient was given an additional four weeks of bed rest. Despite the additional period of bed rest, the restriction of salt, and the use of digitalis and mercurials, minimal physical effort, such as sitting up in bed, resulted in dyspnea, tachycardia, and increased pulmonary edema. At fluoroscopy a hyperdynamic left ventricle with a large pulmonary artery and a questionable intrinsic pulsation consistent with a ventricular septal defect and a left-to-right shunt were found.

Six and one-half weeks after the initial episode of pain a limited cardiac catheterization was done. To avoid irritating the ventricular endocardium no attempt was made to enter the pulmonary artery. The right ventricular pressure was found to be 69/9 mm. Hg, and an oxygen saturation step-up from the right atrium to the right ventricle of 54% to 87% was demonstrated (Table).

It was thought that the clinical picture was compatible with an acquired interventricular septal defect with a left-to-right shunt. Eight weeks after the acute infarction the patient was taken to surgery. He was given endotracheal ether anesthesia, and the chest was entered through a bilateral thoracotomy incision through the fifth intercostal space, with splitting of the sternum and

Catheterization Data

Location	Pressure, Mm. Hg	Oxygen Saturation, %
Superior vena cava		52.7
Mid-right atrium	15/6	53.9
Right ventricle just beyond tricuspid valve)	69/9	87.0
Mean	39	
Early diastolic	0.7	
End diastolic	18.0	
Right ventricle (apex)		86.8

ligation of both internal mammary arteries. The pericardium was found to be markedly adherent, particularly along the posterior of the heart where there was evidence of a recent infarct. Seven 000 nonabsorbable surgical (braided wire) sutures were placed in the right ventricle in a horizontal mattress, interlocking in a row parallel to the interventricular septum in the midportion of the lower right ventricle. A long vascular occluding clamp was then placed below the sutures, forming a pouch of right ventricle between the clamp and the wire sutures, after which an incision was made into the pouch and an index finger inserted into it. With the right ventricle snugly held about the exploring finger through tension applied to the purse-string wire sutures, the occluding clamp was released, and the surgeon was able to feel a marked systolic thrill and jet coming across the midportion of the posterior septal wall adjacent to the right ventricular reflection. The defect seemed linear and about 1.5 cm. long. It was closed by passing special long curved round needles posteriorly through the left ventricle adjacent to the septum, through the septum anterior to the rent, into the right ventricular cavity, and out of the heart through the posterior wall of the right ventricle

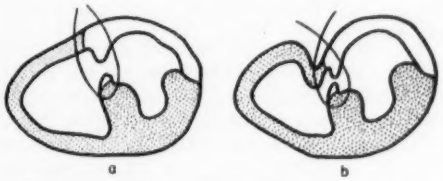

Fig. 2.—(*a*) Diagramatic representations of cross sections of the heart at the level of the septal defect. Normal myocardium is stippled. The posterolateral infarction involving the posterior septum is unstippled. A suture is shown entering the heart through the left ventricle posteriorly adjacent to the septum, passing through the septum anterior to the defect, and leaving the heart through the right ventricular wall adjacent to the septum. (*b*) When the suture is tied down, the septal defect is closed by (1) pulling the margins of the defect together and (2) approximating the right ventricular wall to good septum anterior to the defect.

Fig. 3.—Autopsy examination of the operative site, viewed from the right ventricular side. The three linearly arranged holes are completely buried in the sulcus (indicated by arrows) formed by suturing the right ventricular wall to the septum. Three of the four sutures closing the defects are seen. The right ventricular wall is below the suture line, and the septum, above it. Sutures have been retouched to make them more apparent.

(Fig. 2). After four of these sutures were tied down, the defect was closed by approximation of the right ventricular wall to good septum anterior to the perforation. The thrill and the jet were entirely obliterated, and the systemic blood pressure rose to 120/70 mm. Hg. Previous to this (during the operative procedure) the systemic blood pressure varied between 40 and 90 mm. Hg. Postoperatively, heparin was started.

The patient apparently tolerated the procedure well and continued to improve after surgery. He was more responsive to mercurial injections, and his affect and appetite improved. On the seventh postoperative day he was examined on ward rounds and was thought to be doing well. A few minutes later he suddenly died. The autopsy did not reveal the immediate cause of death until the microscopic sections were examined. These contained the histologic evidence of a fresh infarct in the anteroseptal region of the left ventricle.

The heart weighed 480 gm. There was a dense fibrinous exudate covering the entire external surface. The myocardial thicknesses at the midventricular level were as follows: left lateral, 0.6 cm.; right lateral, 1.2 cm.; right anterior, 0.4 cm.; midseptum, 1.8 cm., and left anterior, 2.0 cm. The tricuspid valve measured 13 cm.; the pulmonic valve, 8 cm.; the mitral valve, 11 cm., and the aortic valve, 9 cm. in circumference. An extensive fibrosed posterolateral infarct extending from the apex to just above the midventricular level was found. It involved the posterior portion of the right and left ventricles and the septum (Fig. 4). The septum in this region was abruptly and markedly thinned. At its posterior margin, beginning at the midventricular level and extending apically for a distance of 1.5 cm., were three linearly arranged holes, each 2 to 3 mm. in diameter. At autopsy no evidence of mural thrombus, of thrombus at the site of repair, or of pulmonary or peripheral emboli was found.

Fig. 4.—Sections of the heart obtained at autopsy. Two apposing surfaces are shown and are the result of a single cut through the apical portion of the heart. The sections have been reflected like the pages in a book, the lower section being the more apical of the two. An extensive healed posterolateral infarction involving the posterior septum is evident. Arrows have been inserted through two of the three linearly arranged holes.

Comment

The incidence of myocardial rupture is reported as 9% of all infarctions, and perforation of the septum as varying between 10% and 18% of all ruptures (0.9% to 1.6% of all infarctions).[1,2,4,9] The development of this complication is marked by the sudden appearance of a loud harsh systolic murmur, maximal in the fourth and fifth intercostal spaces along the left sternal border and radiating as much to the right of the sternum as to the left. A systolic thrill is usually noted over the same area. The clinical course is characterized by the rapid development of intense dyspnea, increasing shock, and progressive right heart failure. The patient may experience the sudden return or intensification of chest pain.

The differential diagnosis of a harsh systolic murmur in a patient with a recent myocardial infarction includes the rupture of the interventricular septum, the rupture of a papillary muscle, the appearance of a pericardial friction rub, and the development of a functional mitral insufficiency. The clinical features of a ruptured papillary muscle significantly resemble those of septal perforation to cause difficulty in distinguishing the two, but suggestive differences have been noted. The murmur of a ruptured papillary muscle is usually musical; it may be louder at the apex than at the left sternal border; it is often diastolic rather than systolic, and it is often not associated with a systolic thrill. The clinical features of a pericardial friction rub and of mitral insufficiency are usually sufficiently characteristic to permit their differentiation from rupture of the septum or of a papillary muscle. Despite the presence of characteristic clinical features, antemortem confirmation of the diagnosis of septal rupture can be made only by cardiac catheterization. In one reported case [6] in which the diagnosis seemed fairly certain on clinical grounds cardiac catheterization failed to reveal the presence of a shunt.

Prior to this case report, catheterization confirmation of acquired interventricular septal defects due to infarction has been reported only twice,[7,10] while at least 12 cases of traumatic septal rupture confirmed by catheterization have been reported.[11,12]

Catheterization of a patient with a fresh infarct carries with it a definite risk, which can, however, be reduced by limiting the extent of the procedure. Arrhythmias occurring during cardiac catheterization are usually the result of the catheter coming into contact with the ventricular endocardium as the catheter is turned cephalad and directed toward the pulmonary artery. Since the diagnosis of acquired interventricular septal defect depends upon the demonstration of a left-to-right shunt in the region of the ventricle, the catheter need only be advanced through the tricuspid valve. Because right ventricular dilatation is usually present, the catheter can be passed well into this chamber before it touches the endocardium.

A significant clinical feature of septal perforation is that death is not sudden, and many extended survivals have been reported.[3,5-7,9,10,13-22] In a review of 91 published cases, Sanders et al.[6] found that survival can be grouped into three categories: those who die in less than one week (54%); those who survive from one week to two months (33%), and those who survive from two months to several years (13%). In almost all reported instances of survival, intractable right heart failure develops early and results in severe morbidity. Approximately one-half of the cases could be considered as possible candidates for surgery.

Pathological examination of septal perforations has indicated that the lesions may be single or multiple and that they usually occur in the apical or central portion of the muscular septum, often adjacent to one of the free ventricular walls. They vary in size from 1 or 2 mm. to 6 cm. in diameter.[6,8,23] They may also consist of a linear tear or a series of holes linearly arranged.[24] In our

experience with this and other cases, the area included, even if there are several defects, is not too extensive to permit surgery by the method described here.

Because of the increased surgical risk presented by these patients, the operation described in this case report has several advantages. Since the defects are usually located low in the septum, a surgical approach which avoids the additional hazards of pump oxygenators and hypothermia seems feasible. It permits closure of the defects either under the direction of the exploring finger or, if necessary, by direct vision, as the great vessels can be occluded periodically, permitting the surgeons to visualize the septum through the ventriculotomy incision. Because the right ventricle is usually dilated, its wall can be sutured to the septum, closing the defects with a minimum of tension and distortion of the heart. The entire procedure can be carried out fairly rapidly, and, as evidenced by the autopsy findings, the defect can be substantially, if not entirely, obliterated.

The indication for the correction of an acquired interventricular septal defect would seem to be progressive deterioration despite optimal medical management. If possible, operations should be delayed until healing of the infarct has taken place. Since 87% of these patients are dead within two months,[6] early operation seems justified whenever a progressive downhill course becomes manifest.

Summary

Interventricular septal rupture complicating myocardial infarction carries a high early mortality. A case is reported in which the diagnosis was confirmed by cardiac catheterization and the defect closed by a new surgical technique.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. ARCHIVES OF INTERNAL MEDICINE, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Calorimetry

The Basis of the Science of Nutrition

RUSSELL M. WILDER, M.D., Ph.D., Rochester, Minn.

Dr. Eugene DuBois, in an obituary of the late distinguished Graham Lusk, wrote that Lusk "had been our strongest link with the old masters and had transmitted to us what was best in the scientific laboratories and academic circles of this and previous centuries. . . . Not only the men who worked in his own laboratory, but those from distant parts of this country and abroad are indebted to him for much of the best parts of their publications." [1] The rather whimsical conceit of Professor Lusk shown here (Fig. 1) is a useful springboard for some of what I have to tell.

The great-grandfather in this genealogy is Antoine Laurent Lavoisier (1734-1794), the founder of modern chemistry, whose head fell under the guillotine of the French Revolution. "It took but a second to cut off his head; a hundred years will not suffice to produce one like it," was the comment at that time of a friend and colleague.[6] From experiments on respiration, which for his day and age were remarkably ingenious, Lavoisier clearly foresaw what his successors established—that the heat of the animal body could be measured by suitable procedures. (He used the melting of ice

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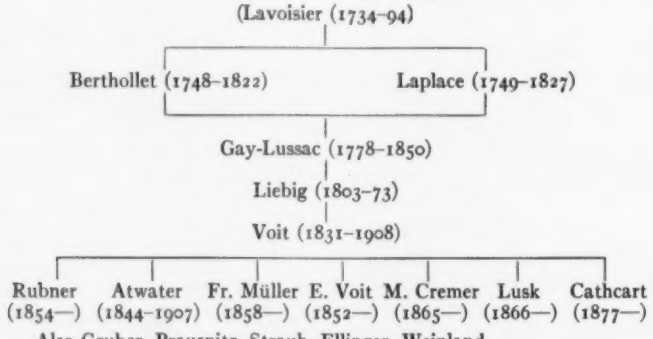

Fig. 1.—Scientific descent of the Voit school.

for his direct calorimetry and a copper mask, into which the subject breathed, to collect expired air for measurements of carbon dioxide.)

Two associates of Lavoisier, Claude Louis Berthollet (1748-1822) and Pierre Simon LaPlace (1749-1827), both became distinguished scientists. The Emperor Napoleon I is said to have attended the lectures on chemistry of Berthollet and to have taken him with other academicians on his campaign in Egypt. It was LaPlace who first suggested the use of statistics in medical and other biologic investigations.

Next in the line of descent is Joseph Louis Gay-Lussac (1778-1850), a pupil of Berthollet, who became the greatest chemist of his time, and into this stimulating Parisian atmosphere in 1822 came Justus von Liebig to study under Gay-Lussac.

Baron Justus von Liebig (1803-1873) carried the torch of biologic chemistry to Germany, where in Giessen and later in Munich he came to be the greatest organic chemist of his day. He it was who first made precise analyses of foods and clearly showed that their main constituents could be classified in three categories—carbohydrates, fats, and proteins. Among Liebig's many contributions was the demonstration, largely through the work of his pupil Carl von Voit, that body heat results from the combustion of food and can be measured by analysis of expired air for carbon dioxide and of excreta for nitrogen. Of the greatest significance for later studies of metabolism was his demonstration that protein breakdown can be ascertained from the nitrogen content of urine and feces.

Carl von Voit (1831-1908) became professor of physiology in Munich, and he taught many pupils who, like him, in time became giants in the field of metabolism. Among those named on Lusk's genealogy are Max Rubner, Wilbur Atwater, and Friedrich Müller, who came to be considered the most eminent clinician of his day. Also named are Erwin von Voit, a brother of Carl who was noted for his studies of starvation and the protein-sparing action of fat, and Graham Lusk himself, late professor of physiology in the Cornell University Medical College.

If you care to carry the descent still further, many of you will find yourselves included in the genealogy. Ringer, Chambers, Murlin, DuBois, McCann, Barr, Shorr, and several other later great figures were among Lusk's pupils. Their own pupils are all around us. Francis G. Benedict, director of the nutrition laboratory of the Carnegie Institution in Boston, was an associate of Atwater in his studies of respiratory metabolism, and among Benedict's disciples was the late Walter M. Boothby, who provided inspiration at the Mayo Clinic. Also R. T. Woodyatt, of the Otho S. A. Sprague Institute in Chicago, studied under Friedrich Müller, and the torch he handed on to Randall G. Sprague and me has been passed by us, in turn, to those who later became our associates.

We left Carl von Voit as a pupil and successor of Liebig. His famous respiration calorimeter, shown here (Fig. 2), was built with the aid of Max von Pettenkofer, then an instructor in Liebig's laboratory. The illustration is from Tigerstedt's "Human Physiology." This is the smaller apparatus of Voit and Pettenkofer. They had previously devised equipment large enough to be used in the study of human beings. Financial assistance was obtained by them from King Maximilian II of Bavaria. The cost was 8,000 guilders, a sum not less than $10,000 or $20,000 now. This was one of the many instances of governmental interest, at that time and later, which enabled Germany to capture and retain for many years her remarkable leadership in science.

Before we continue with the contributions of the Voit school, mention must be made of the earlier work of F. W. Bidder and C. Schmidt. Working in relative isolation at Tartu in Estonia, Bidder and Schmidt made many important observations, and their book "Die Verdaungsäfte und der Stoffwechsel" was referred to by Voit as a

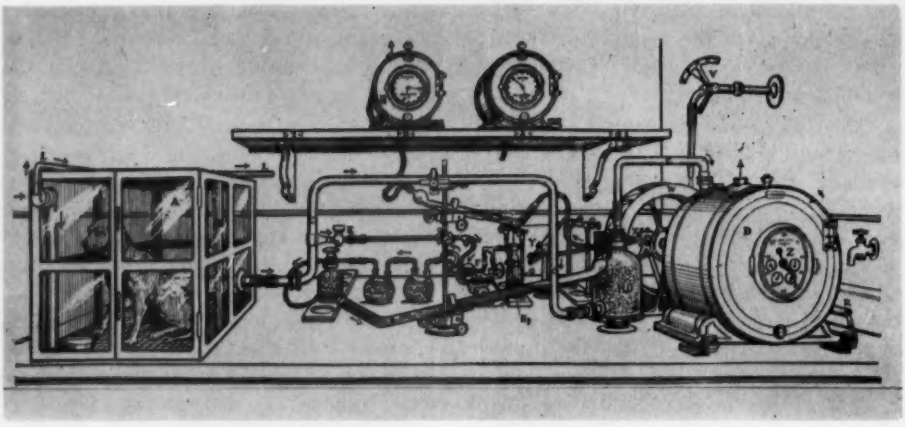

Fig. 2.—The smaller respiration apparatus of Pettenkofer and Voit. Air enters the cage (*A*) at the upper left-hand corner. It is drawn out through openings in the tube (*B*) (spaced so as to insure thorough diffusion), through the tube (*C*) and the large H_2O flask, where it is saturated with moisture, to the gas meter (*D*) where it is measured. The meter is driven by a water wheel (*W*) rotated at a uniform rate of speed by a constant head of water pressure (*V*). At *E* a side tube leads off from *C*, conveying a sample of cage air for analysis. This air is drawn through a mercury valve (*F*) by means of the mercury pump (*G*). The latter is operated by the mechanism (*X*, *Y*), connected with the water wheel. From the valve (*F*) this air passes through two H_2SO_4 flasks and is then saturated with moisture so as to prevent loss of water from the $Ba(OH)_2$ tubes. Of course the air, as it leaves the $Ba(OH)_2$ tubes, is saturated with moisture, and is measured by the small gas meter (*H*), just as in the case of the large meter, while in this saturated condition. A duplicate sample is led off at the same time through another branch of the tube (*E*) and through another system of vessels to the gas meter at 3. Through the branches of the tube (*L*) duplicate samples of the air which enters the cage are drawn in the same manner to similar valves and then through similar vessels and tubes to meters placed at 1 and 4 (Tigerstedt's "Human Physiology").

veritable mine of information. They also were first in formulating the concept of basal metabolism. DuBois [2] has quoted them, "For every species of animal there is a typical minimum of necessary metabolism which is apparent in experiments when no food is given." Likewise not to be neglected are the Parisians Regnault and Reiset who, as early as 1847, described an apparatus for the measurement both of carbon dioxide production and of oxygen consumption. They used small animals in closed containers but would have turned to experiments on man had funds been available. They recognized the significance of the respiratory quotient CO_2/O_2 and the effect on this of different foods. They also were the first to note the relationship of the amount of oxygen absorbed to the area of the surface of the body, noting that the metabolism in relation to weight is greater in sparrows than in chickens.

Lusk regarded Max Rubner (1854-1932) as the most eminent of Voit's many distinguished pupils. It was Rubner who first examined systematically the caloric value of the common foods and proposed as calorie equivalents for carbohydrates, fats, and proteins the figures 4.1, 9.3, and 4.1. These Rubner standards have been generally employed throughout the world and during both world wars were used to calculate, for import-export estimates, the food requirements of nations.

Moreover, in 1891, Rubner constructed the first machine which precisely measured body heat directly with controlled precision. To it he attached a Pettenkofer-Voit respiration apparatus for the measurement of expired carbon dioxide. His early studies were conducted with dogs. His first experiment lasted 45 days and gave results as follows:

Calculated from the materials oxidized in the body	17,406 Cal.
Actually measured from the animal calorimeter	17,349 Cal.
Difference	0.2%

Here then was proof of the application in biology of the law of the conservation of energy, as pronounced by Robert Mayer and independently by the great Hermann Ludwig von Helmholtz in 1842 and 1847, respectively. It had been suggested by Lavoisier's experiments of the preceding century.

Rubner's findings were soon confirmed by others, including the Americans Wilbur Atwater, F. G. Benedict, Graham Lusk, John R. Murlin, and Eugene Floyd DuBois.

Wilbur Atwater (1844-1907) studied under Rubner as well as under Voit. He became chief of the experimental stations of the United States Department of Agriculture and with A. P. Byrant developed and published, in 1895, through the Government Printing Office, tables of the chemical composition of American foods. These, with subsequent revisions, have been in general use since then.

Within a year of the report, in 1891, of Rubner's elegant experiment in which a dog was studied in a calorimeter for a period of 45 days, Atwater began work on a calorimeter for the direct measurement of the production of heat in human beings. He had access to government appropriations as well as assistance from an eminent physicist, E. B. Rosa. After years of labor, an apparatus was constructed so nearly perfect that the results of experimentation on man revealed a correspondence between chemical-indirect and physical-direct calorimetry as good as that obtained by Rubner.

In the original calorimeter of Rubner and in that of Atwater and Rosa the Pettenkofer-Voit open-circuit apparatus was attached for the measurement of carbon dioxide and water vapor. Soon afterward, however, Atwater, with F. G. Benedict, was able to develop a closed-circuit apparatus which made it possible to measure oxygen consumption, thus permitting calculation of the respiratory quotient (CO_2/O_2). In this closed-circuit apparatus the subject is confined in an airtight insulated box and rebreathes expired air after the removal of carbon dioxide from the air and the addition to the air of an amount of oxygen sufficient to maintain the volume of gas in

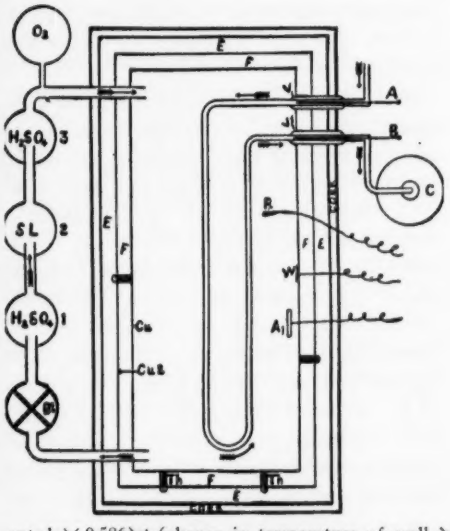

Fig. 3.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter (Lusk,[5] p. 70).

Ventilating system: O_2 indicates oxygen introduced as consumed by subject; *3*, H_2SO_4 to catch moisture given off by soda lime; *2*, soda lime to remove CO_2; *1*, H_2SO_4 to remove moisture given off by patient; *Bl*, blower to keep air in circulation.

Indirect calorimetry: increase in weight of H_2SO_4 (*1*)=water elimination of subject; increase in weight of soda lime (*2*)+increase in weight of H_2SO_4 (*3*)=CO_2 elimination; decrease in weight of oxygen tank=oxygen consumption of subject.

Heat-absorbing system: *A* indicates thermometer to record temperature of ingoing water; *B*, thermometer to record temperature of outgoing water; *V*, vacuum jacket; *C*, tank for weighing water which has passed through calorimeter each hour; *W*, thermometer for measuring temperature of wall; A_1, thermometer for measuring temperature of the air; *R*, rectal thermometer for measuring temperature of subject.

Direct calorimetry: average difference of *A* and *B* × liters of water+(grams of water eliminated × 0.586)±(change in temperature of wall × hydrothermal equivalent of box)±(change of temperature of body × hydrothermal equivalent of body)=total calories produced; *Th* indicates thermocouple; *Cu*, inner copper wall; *Cu*$_2$, outer copper wall; *E* and *F*, dead air spaces.

the box. The heat evolved was computed on the basis of the change in temperature of water circulating in pipes through the box and also on the basis of the amount of water vapor lost. A diagram of the apparatus (Fig. 3) shows the line of bottles for the absorption of water vapor by sulfuric acid and of carbon dioxide by soda lime. These bottles were weighed and replenished hourly.

Shortly after the development of the Atwater-Benedict calorimeter, H. B. Williams, under Lusk's direction, made further improvements in the apparatus and built one for the physiological laboratory of the Cornell University Medical College in New York City. With this equipment Lusk was able to conduct experiments on dogs, babies, and dwarfs. In 1912, at Bellevue Hospital, came the construction of the Russell Sage calorimeter, an apparatus large enough to permit a human being to lie quietly in bed "as comfortably as in a sleeping car." The immediate direction of experiments on human subjects was the work of Eugene F. DuBois. The results obtained revealed again complete agreement between direct and indirect calorimetry, not only when healthy men were subjects but also when patients with fever and other disease symptoms were involved.

The experiments with the respiratory chambers and calorimeters were elegant but time-consuming, and their use was limited to observations made in the laboratory. A desire for wider application led to trial of other procedures. The desire was prompted largely by the need for knowledge of food requirements of populations subjected to limitation of food by war or other causes, necessitating rationing. One such simplified procedure was the measurement of expired water vapor.

The closed-circuit calorimeter had revealed that about one-quarter of the heat eliminated by a subject was accounted for by the water vapor absorbed by the first sulfuric acid bottle of the absorber line. (Lusk,[5] p. 71: "at 20° C. 0.586 calorie is contained as latent heat in gram of vaporized water.") This is *insensible perspiration*, and it carries us back as far as Sanctorius of Padua (1561-1636). In his Aphorism V, Sanctorius referred to what he termed insensible perspiration through the mouth, "which usually in the space of one day amounts to the quantity of half a pound of water, as may plainly be made to appear by breathing upon a glass." The constancy of insensible perspiration was so great in resting subjects that on the basis of it alone Benedict and Root (1926) could predict the basal metabolism. L. H. Newburgh resorted to this factor as a means for estimating energy exchange. The only equipment necessary for such a procedure is an accurate scale or balance. In experiments involving much physical activity, however, an error is involved of such magnitude as to make the method undependable.

Nathan Zunz (1847-1920) was the pioneer in devising a *portable* apparatus for measuring metabolism in human beings. He used a mask for collecting expired air for analysis, and he tested men resting or walking. His pupil Magnus Levi carried the apparatus to the hospital, made observations in the presence of many diseases, and introduced the term *Grundumsatz*, which DuBois and Lusk translated as "basal metabolism."

In later years, interest in the basal metabolic rate came to occupy attention to such a point that the observation of energy exchange for long periods was neglected. Nevertheless, in 1924, A. V. Hill made a number of observations of men at work, using for the purpose a battery of Douglas bags. The Douglas bag is carried on the subject's back, and he breathes into it through a face mask or mouthpiece. The bag holds from 30 to 100 liters. The volume of air accumulated is measured in a meter, and samples are then removed for analysis. A number of similar studies were conducted by Hill and others, and, in an effort to arrive at total calorie requirements of one day, a summation procedure was employed.

This involved measurement of the time spent at rest and at the various activities of the waking hours, determination of the metabolism at rest and at each of the activities, and, by addition, arrival at the total for the day.

Keys,[3] in 1949, considered that estimates of total (24-hour) expenditure of energy based on data of this type were unreliable; nevertheless, collection of such data has continued on an extensive scale and with some refinement. What has come to be regarded as a much more satisfactory apparatus than the Douglas bag is a very light (less than 4 kg.) gas meter into which the subject breathes through a mouthpiece. A continuous sample (0.1%) is diverted from the main line to a rubber bag. The meter gives the total respiration. Only the contents in the bag are analyzed. The apparatus was developed by Kofrányi and Michaelis in 1941 and has been improved by them and others of the Max Planck Institute für Arbeitsphysiologie at Dortmund, Germany.[4,7] Extensive study with this apparatus has been conducted at Dortmund and by Passmore, Durnin, and others at Edinburgh and Glasgow.[8-10] The results still leave much to be desired, for obviously it is impossible to extend a respiration experiment into hours or days when the subject has to breathe through a mask or mouthpiece. Furthermore, with only short periods of direct observation, the investigator still is dependent on a timing of activities, with its attendant unreliability.

My personal interest in chamber calorimetry stems from a long-existing distrust of evaluations of total energy exchange based, as they so frequently have been, on short periods of actual observation. I always have wanted to see continuous determinations of gas exchanges extend over days and weeks, particularly when the studies involve investigation of diseases. Because of the intricate computations required for such experiments and the cost involved in the equipment and its maintenance, my ardor never was sufficient to lead me to undertake chamber calorimetry at the Mayo Clinic. When, however, on my retirement from the clinic I became director of the Institute of Arthritis and Metabolic Diseases, then under development at Bethesda, I proposed the inclusion of the necessary facilities for chamber calorimetry in the Clinical Center at that place. The Clinical Center at that time (1950) was in the process of construction. It has taken nearly seven years, and somewhat more money than I estimated, to build this chamber, but at long last it has been completed, and studies with it now are under way.

We were fortunate in finding through Dr. Ephraim Shorr, who, as was mentioned, was a pupil of DuBois, just the man to see us through this undertaking, namely, Dr. G. D. Whedon. Dr. Whedon had had training for research under Shorr in the Cornell University Hospital and possessed the very necessary patience and the capacity for persistence required for such studies. In the planning of the chamber, assistance was obtained from a number of consultants. They included Dr. DuBois, Dr. Walter M. Boothby, Dr. L. H. Newburgh, and especially Dr. James D. Hardy, who then was associate professor of physiology at Cornell. Hardy had been working with a smaller calorimeter, which he had designed for use with animals and by which the previous laborious weighings and refillings of the bottles of sulfuric acid and soda lime on the absorber line had been replaced with continuously recording electronic-stream gas analyzers. These analyzers automatically write their findings on rolling strips of paper, and, as I watch them perform, I constantly am reminded of those lines from the "Rubaiyat": "The Moving Finger writes; and, having writ, moves on: nor all your Piety nor Wit shall lure it back to cancel half a Line, Nor all your Tears wash out a Word of it."

The Bethesda working team has consisted of the clinical investigator, G. D. Whedon; the physiologist, R. H. Thompson, and the physicist, E. H. Huber, now replaced by

R. Moore. E. R. Buskirk and L. Lutwak recently have joined the group. I was delighted to find Dr. Buskirk at Bethesda, since I was aware of the important work he had been doing with the Environmental Protection Division of the Quartermaster Department. From this point onward what I have to say about this chamber is taken largely from the description of it presented last year at the meetings in Chicago of the Federation of American Societies for Experimental Biology.

Whedon and his associates [11] at Chicago brought out, as I have herein, the point that, although extensive studies of numerous influences on the basal rate of metabolism have been carried out, relatively little recent interest has been directed toward precise measurement of the effect of these influences on the total energy exchange.

In the apparatus described by Whedon and his associates, modified from that devised by Hardy for studies with animals, the use of continuously recording stream-gas analyzers has provided information of two different types.

First, the system has sufficient rapidity of response to reveal minute-to-minute patterns of variation in the consumption of oxygen and the excretion of carbon dioxide. This feature of the technique permits analysis of the gas exchange at all stages of energy expenditures during exercise and thus can measure working efficiency with greater reliability than has been possible heretofore.

Second, information is provided covering the continuous expenditure of energy over many hours and days, which should enable studies to be made of the influence of a wide variety of environmental, hormonal, nutritional, and other factors on total energy metabolism.

The metabolic chamber is sufficiently commodious to permit a human being to lead a fairly normal life in it. He sleeps there, arises, performs his toilet, has his food, walks (on a treadmill) to and from his work, and engages in any sedentary occupation decided upon. At present the chamber is an open-circuit indirect calorimeter; equipment for the direct measurement of heat may be added later. Even as it is, however, not only carbon dioxide but also oxygen is measured, and thus all the data required for minute-to-minute calculation of respiratory quotients are obtained. Fresh air enters the air-conditioning compartment, and there it is equilibrated to the temperature and humidity desired for the experiment contemplated. Close control of temperatures can be maintained through a range of 5 to 49 C, and relative humidities can be made to prevail between 10% and 95%, concomitant with most of these temperatures. Air recirculates through the chamber at a rate of 1,300 cu. ft. per minute, but, by means of a large area of inlet ports which cover the entire ceiling and an exhaust area that covers one-half of one wall, the air velocity in the chamber is maintained at the very low rate of 50 ft. per minute. Noise has been reduced to a minimum. The sound level in the chamber, with all air-conditioning and other apparatus running, is less than 40 db. The leakage of air in or out of the chamber is negligible.

Air flows from the chamber into a collection hood or helmet placed over the subject's head and shoulders, and thence the air is conducted by flexible tubing from the chamber through a vacuum line to an air-volume meter. This hood or helmet interferes very little with freedom of motion. The rate of air flow through the vacuum line is close to 100 liters per minute, which approximates 10 times the subject's resting tidal volume. Samples of the air from the main line are carried through the oxygen and carbon dioxide analyzers at a constant rate of flow of 50 and 100 cc. per minute. Valves in the line are so arranged that the analyzers may periodically tap air directly from the chamber to establish reference or base lines. The gas analyzers are tested before and after each experiment by causing known constant volumes of either carbon

dioxide or oxygen to flow into the empty hood from a calibrated spirometer.

The helmet mentioned is of vinyl plastic. It is provided with a flexible plastic "elephant's trunk" through which the subject can scratch his nose, shave, wash, brush his teeth, and take a liquid diet with a straw. A microphone permits two-way conversation between the subject and persons at the control desk. No serious objection can be taken to limiting the diet to a liquid mixture. This is made of milk, cream, eggs, and sugar for consumption through a straw and has the great advantage of being in a form that can be analyzed easily.

Relative humidity is determined with Aminco electric hygrometers. Carbon dioxide is analyzed by a Baird stream analyzer, with use of the infrared absorption principle and a bolometer bridge detector. Oxygen is determined with a Beckman analyzer, the output being fed through a direct-current amplifier to the Speedomax recorder, on which also is recorded the relative humidity. Several illustrations of the chamber and equipment have already appeared. (Metabolic Chamber, *Pub. Health Rep.* 72:1084-1086 [Dec.] 1957.)

So far as I can ascertain, there is as yet no published description of a study—even in the Soviet Union—of the long-term continuous type (on human beings) that Dr. Whedon's group now is undertaking with this apparatus. Closely related studies, however, are under way in several laboratories, and extremely important work is in progress at the National Cancer Institute and at the Naval Medical Research Institute. One of the most provoking problems in nutrition relates to energy requirements in the presence of obesity and refractory thinness. How frequently we hear the comment that this or that person loses no weight even though he follows a diet or that someone eats enormously, yet gains no weight. With the apparatus here assembled, the answer to such problems may be had. So, too, in cancer there seems to be a question of whether energy exchange can be measured reliably with the indirect method alone. Dr. Whedon expects to get at this problem in time and also to study the influence of other pathologic conditions on total energy exchange. Observations of minute-to-minute changes in oxygen consumption, made possible by these electronic stream-gas analyzers, and studies of oxygen debt, with and without retention of carbon dioxide, ought to be revealing. Similarly, the use and dissipation of energy by the living organisms (bacteria) in the intestinal tract perhaps can be elucidated. Current enzyme studies of intermediary metabolism have shown that many stages of metabolism involve transfers of energy from one molecule to another, in which case there must be excretion of materials that may or may not represent the energy received as food. These and other problems will lend themselves to study with the equipment here assembled.

The work is tedious but promising. Lavoisier would rejoice in it; so also would Voit. It was Voit who taught, "One case carefully investigated is of greater worth than hundreds casually examined."

Mayo Clinic.

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Contributions of Basic Science to Modern Medicine

Current Views on the Pathogenesis and Treatment of Wilson's Disease

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. . . arrive at the new truth with hands blood-stained from the slaughter of a thousand platitudes.
Ortega y Gasset, "Revolt of the Masses"

The object of this article is to attempt to give a concise account of recent advances in our understanding of the underlying biochemical disorder in hepatolenticular degeneration, not to describe the clinical manifestations and the various diagnostic pitfalls to which these may give rise. In the light of this new knowledge reference can be made to the theories of pathogenesis and to progress in the treatment of the disease. Accounts of the clinical course of the illness have been given in recent review articles,[1,2] and, of course, Wilson's original monograph[3] must be consulted by all interested in the condition.

As in other rapidly advancing fields of knowledge, the literature on Wilson's disease contains contradictions and discrepancies which are hard to reconcile. Similarly, there are divergent theories to explain the recorded biochemical disorders. Certain facts are, however, firmly established, and these can, with advantage, be considered first.

Copper Metabolism

Consistent but scattered reports, mostly in the German literature, have shown for some time that a study of copper metabolism in patients with Wilson's disease might well be rewarding. So it proved, for Cumings[4] showed that the livers and brains from three patients dying of the disease all contained abnormal amounts of copper. This observation has been amply confirmed and extended; most tissues except heart and striated muscle contain excess copper.[5] In the urine, too, the concentration of copper is very high,[5,6] the normal figure of up to 50μg. a day being exceeded ten- to twenty-fold. In the light of these findings the reports of high concentrations of the metal in plasma were not unexpected.[7,8] Subsequently, however, it was established that the serum copper was almost invariably low, sometimes very low, in patients with the disease.[5,9] An apparently unrelated observation in the field of protein chemistry now became highly relevant. In 1948, Holmberg and Laurell[10] showed that 95% of copper present in normal serum was tightly bound to a blue α-globulin, ceruloplasmin, a protein with a molecular weight of 151,000, each molecule carrying eight atoms of copper. In the serum of patients with Wilson's disease, this protein is either deficient in concentration or absent.[11] This finding is now believed to be the most constant single biochemical abnormality of the disease.[5,12] Further researches have shown that, as a consequence of the deficiency of ceruloplasmin, an abnormally high percentage of serum copper is loosely complexed to albumin and able to react directly with diethyldithiocarbamate.[5] In Wilson's disease, then, the total serum copper is low, the globulin-bound copper is very low, and the "direct"-reacting copper is significantly elevated.

Despite the considerable daily loss of copper in the urine, a great excess of the metal accumulates in the tissues. From this it must be concluded that the patients are in

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positive copper balance. This indeed has been confirmed by careful metabolic studies,[5,13] though the figures of 1 to 2 mg. a day quoted by Cartwright's group can hardly be accepted, as these would mean that by the age of 20 the body would contain 7 to 15 gm. of copper, figures far in excess of any yet recorded. Corresponding with the positive copper balance, there is a decreased amount of copper in the stools. This is probably due to increased absorption rather than to decreased excretion into the intestine, for it has been shown that the copper concentration in bile is within normal limits.[14]

The Renal Lesion

In addition to the derangements of copper metabolism already described, abnormalities of renal function are common in patients with Wilson's disease. Amino-aciduria was first described by Dent,[15] but the renal origin of this was only established later.[16] More recently other abnormalities of tubular function have been identified leading to a raised renal clearance for glucose, phosphates, and urates. Nor does the glomerulus escape; the effective renal plasma flow and glomerular filtration rate are frequently reduced, and proteinuria is not uncommon.[7] However, unlike the abnormalities of copper metabolism already described, the renal lesion is not an invariable accompaniment of the disease. Bearn[1] found an increased ratio for the clearance of α-amino nitrogen to inulin in only seven to nine patients, and numerous cases of fully developed Wilson's disease have been described with normal urine amino acids.[18]

Biochemistry of Wilson's Disease

Reference must now be made to certain more controversial points. The nature of the copper-protein linkage has been challenged by Cumings, Goodwin, and Earl.[19] The work of Holmberg and Laurell,[10] identifying ceruloplasmin, an α-globulin, as the copper-carrying protein in normal serum, has already been mentioned. By following the fate of injected radioactive copper, Bearn and Kunkel[20] later showed that the copper was bound to albumin for a short time after injection, but after 12 hours it was firmly attached to an α-globulin with the same electrophoretic motility as ceruloplasmin. Furthermore, in Wilson's disease this transfer did not occur. The labeled copper remained attached to albumin for as long as the short half-life of the isotope permitted its fate to be studied. Now Cumings and his group used a salting-out procedure for protein fractionation and found, in normals, that most of the copper was in the β-globulin fraction, although small amounts of copper were also attached to α- and γ-globulin. They also found a similar distribution of globulin-bound copper in serum from patients with Wilson's disease, but they agreed that in these most of the copper was attached to albumin. Another difficulty raised by their work concerned the oxidase activity of plasma. Ceruloplasmin, in vitro, acts as a weak oxidase for p-phenylenediamine, and it was to be expected that the oxidase activity of plasma would be found with the α-globulins, but in Cumings' fractions it appeared to be located as a β-globulin. In Wilson's disease serum, although β-globulin-bound copper was present, no oxidase activity was detected. This group criticized the work of Bearn and Kunkel on the ground that they studied the serum too soon after giving the radiocopper, that is, before the final distribution of the metal among the protein fractions was achieved. However, their own work is subject to the far more serious criticism that the procedure of salting-out employed did not give an electrophoretically pure separation of the proteins.

The nature of the urinary copper has also been the subject of speculation. Uzman[21] has described a specific peptide which, he suggested, carries the copper, but this awaits confirmation.[18] Similarly, he found a specific copper-binding peptide in the liver, and this he believes may be present in other tissues of patients with Wilson's disease,

an observation which at present remains unconfirmed.[22]

The variable chemical and clinical response to treatment with intramuscular dimercaprol (Bal) is another puzzling feature of Wilson's disease, but this will be discussed in more detail later.

Isotope studies with radioactive copper Cu^{64} have also added to our knowledge. There is a remarkable agreement among the findings of the various groups using the tracer technique. Briefly, their findings may be summarized as follows. Orally administered copper is taken up at a comparable rate by patients and controls, and initially the copper is bound to serum albumin. In normals the concentration of albumin-bound copper soon starts to fall and after 24 hours is very low, at which time there is a secondary rise in the α-globulin with an electrophoretic motility similar to ceruloplasmin. In patients with Wilson's disease there is a much slower rate of fall in serum radioactivity, the secondary rise does not occur, and no globulin-bound radiocopper can be detected during the time of study permitted by the short half-life of the element. The pattern of excretion of the injected copper also differs in the two groups; the normals excrete much in the stools and little in the urine, while the patients excrete much in the urine and relatively little in the stools and retain a considerably higher percentage of the dose.[23-25] Recently it has been shown that radiocopper is rapidly concentrated by the normal liver, 90% of the dose being present in the organ after 10 hours; thereafter the concentration falls steadily. In Wilson's disease the initial uptake by the liver is slow, but it is continuous for at least 50 hours.[26]

Comment

This summarizes knowledge of the biochemistry of Wilson's disease and refers briefly to some more controversial points at issue. The synthesis of these facts into a coherent theory, able to account for them all, is a very much harder task. Indeed, it is scarcely possible at the present time. The most widely accepted hypothesis places the deficiency of ceruloplasmin as the key to the problem, the genetically determined metabolic error,[9] which is the inability of the body to synthesize sufficient amounts of this specific serum protein.[27] As a result, an excess of diffusible copper is present in the blood and free to enter the tissues, principally the liver, brain, and kidneys. Accumulation of copper in the liver leads to cirrhosis; in the brain, to the death of neurones in the basal ganglia, cerebullum, and cortex, and in the kidneys, to tubular damage and failure to reabsorb amino acids, phosphates, urates, and glucose, a lesion similar to that caused by lead and other heavy metals. The deposit of copper in the cornea gives rise to the characteristic Kayser-Fleischer rings.

Certain difficulties must be considered before this theory can be accepted. Why, for instance, does the disease usually present as hepatic failure in the younger age groups and as nuclear degeneration in adolescents and adults? There is a possible explanation. The liver in infancy has a high copper content which decreases as the animal develops, while the newborn infant is severely deficient of ceruloplasmin, a state of affairs which persists into later life only in Wilson's disease. Should the copper content of the diet be high in the first few years of life, the excess would be taken up preferentially by the liver, leading to the rapid onset of hepatic failure, for the copper ion is known to be very toxic to many enzyme reactions. If, however, environmental conditions are more favorable, the patient may not be exposed to what are, to him, dangerous concentrations of the metal until the liver is no longer so vulnerable, and the brain and other organs will then come to share the damage. Elsewhere I have pointed out that copper accumulates most in those organs with the greatest Krebs (tricarboxylic acid) cycle activity and that the metal may well become bound to one of the -SH enzymes present in the cycle.[28]

Why, it might be asked, should a simple deficiency of ceruloplasmin lead to excess absorption of copper from the intestine? Recent work by Scheinberg [29] has thrown light on this. Half of the copper atoms bound to ceruloplasmin can dissociate in the presence of excess ascorbic acid, i. e., under reducing conditions. Such conditions may exist in the capillaries of the intestinal wall. This would result in a sharp rise in the concentration of ionized copper in the plasma, above the level found in the intestinal lumen, and copper would not be absorbed. In Wilson's disease, owing to the deficiency of ceruloplasmin, such a mechanism cannot operate and copper in the intestine will always be likely to enter the body. But perhaps the last, and greatest, difficulty in accepting the ceruloplasmin theory of pathogenesis lies in the poor or absent correlation between the concentration of the protein in patients and the clinical course of the disease. In 39 patients studied, Cartwright [30] has found this correlation so poor as to cast grave doubts on its significance. Furthermore, attempts to restore to and maintain the ceruloplasmin level at normal have not, as yet, resulted in any detectable clinical improvement.[1]

As an alternative to the theory that the deficiency of ceruloplasmin is the key to the pathogenesis of the disease, it has been suggested [21,31-33] that the primary defect is in intracellular protein metabolism. This leads to the formation of proteins with a high avidity for copper, which accumulates, passively, in the cells. The earliest detectable abnormality is amino-aciduria, and the deficiency of ceruloplasmin is a secondary and unimportant phenomenon. To support these views, Uzman [32] has described a remarkable family * in which four siblings died of Wilson's disease while five asymptomatic siblings all had a heavy amino-aciduria. Furthermore, he reported finding a specific copper-binding peptide in the urine of these and other patients with Wilson's disease, and in a single liver biopsy specimen he found an abnormal protein with a very high avidity for copper. Others have not agreed that amino-aciduria is the first detectable abnormality, nor, indeed, is it always present even when the disease is fully developed.[5,18,34]

* Some unpublished data of O. Frossman and C. B. Laurell tend to suggest that this family is not suffering from classical Wilson's disease.[1]

Treatment

If it is accepted that (*a*) tissue damage in brain and liver is due to accumulation of copper and (*b*) copper accumulates as a consequence of the deficiency of ceruloplasmin, then it follows that therapy should be aimed at either removing the former or replacing the latter. If, on the other hand, the role of copper as the toxic ion producing symptoms is denied, then we must admit to therapeutic bankruptcy.

Various agents are now available which will mobilize body copper, of which dimercaprol was the first [35] and is still the most widely used. Despite the experience which has accumulated, views as to its usefulness are still conflicting. Cumings [4] found that only two out of four patients had a good clinical or biochemical response. On the other hand, Denny Brown [36] reported that under treatment with dimercaprol in short courses every two to three months, "any evidence of disorder of hepatic function that has been present has subsided under treatment" and "all types of neurological symptom responded to elimination of the relatively small fraction of accumulated copper." Each of his courses of dimercaprol was calculated to remove 3 to 4 mg. of copper. Such treatment, if persevered with, would benefit most patients in time, and even the Kayser-Fleischer rings would clear. He, himself, had excellent results with 12 patients. On the other hand, Bickel,[18] who studied eight patients with Wilson's disease, found that in four dimercaprol had to be stopped almost at once because of serious toxic reactions; no patient improved, and one, who was asymptomatic when treatment was started, actually went downhill rapidly and died. The truth probably lies between these two series; some patients will respond,

some will not, and others will have toxic reactions which preclude further treatment.[37]

One of the more curious features of treatment with dimercaprol is the poor correlation between the clinical response and the magnitude of the resulting cupruresis. This suggests to me that the beneficial action may have nothing to do with the removal of copper but with the supply of readily available -SH groups for intermediary metabolism, as has been demonstrated for diabetes mellitus.[38] The painful nature of the dimercaprol injection and the high percentage of toxic reactions [18,37] have led to a search for other chelating agents. Of these, edathamil (Versene) is one of the most active when given by vein in doses of 1 to 2 gm. per day, but when it is given by mouth little is absorbed and the results are somewhat unpredictable.[13,18] The intravenous administration of protein hydrolysates or amino acids will also increase the excretion of copper, as will a high-protein diet or cortisone. A simple and valuable adjunct is to prevent copper absorption from the intestine by giving either potassium sulfide (20 mg.) after meals or a carbacrylamine resin (Carbo-Resin).[12] Recently the search for a powerful chelating agent, active when given by mouth, has led to the use of penicillamine (β,β-dimethyl cysteine).[28] Given orally in doses of 1 to 2 gm. daily, this compound will produce a much greater cupruresis than any yet used,[1,28] but its clinical usefulness has yet to be proved. However, both Cartwright [30] and Bearn [39] now believe that penicillamine is the treatment of choice for patients with Wilson's disease.

As an alternative therapeutic approach, attempts have been made to restore the ceruloplasmin level to normal. Giving estrogens will indeed raise the ceruloplasmin concentration, not only in normals [40] but also in some patients with Wilson's disease,[1] but, as after the intravenous administration of the purified protein,[18] no obvious clinical benefit has been observed. Possibly the copper carried in with the infused ceruloplasmin (approximately 0.3%) may more than counterbalance the benefit derived from the enzyme. Perhaps an infusion of the apoenzyme is what is required, but the technical difficulties to be overcome before this can be done are formidable.

Summary

Treatment of hepatolenticular degeneration is at present confined to removing copper from the body or to reducing its absorption from the intestine. Of the available "decoppering" agents, dimercaprol (Bal) is the cheapest and most readily obtainable, but it has many unwanted side-reactions; penicillamine is the most powerful and, so far, is without recorded toxic reactions, but it is expensive and its value in long-term treatment has yet to be fully assessed.

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Addendum

Addendum added in proof. I have recently learned that three cases of Wilson's disease on treatment with penicillamine, have developed granulocytopenia. This is probably a consequence of the known pyridoxine antagonism of penicillamine and suggests that in long term treatment with this compound pyridoxine should be added to the therapeutic regimen.

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News and Comment

ANNOUNCEMENTS

Examinations by American Board of Nutrition.—The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition during the week of April 12-18, 1959, in Atlantic City, N. J. Candidates who wish to be considered for these examinations should forward applications to the Secretary's Office not later than March 1. Application forms may be obtained from the Secretary, Robert E. Shank, Department of Preventive Medicine, Washington University School of Medicine, Euclid and Kingshighway, St. Louis.

Books

EDITED BY WILLIAM B. BEAN, M.D.*

The Mind and the Eye. By Agnes Arber, M.A., D.Sc., F.R.S., F.L.S. Price, not given. Pp. 146. Cambridge University Press, Bentley House, 200 Euston Rd., London, N. W. 1, 1954.

From time to time a thoughtful scientist is able to set down accumulated experiences seen and felt perceptively in such a way as to stimulate people in widely separate fields of science or in other fields of endeavor. Since medicine is the oldest field of biology, it stands to profit from a consideration of biology as seen from the viewpoint of a learned and perceptive biologist, Agnes Arber, whose field happens to be that of botanical morphology. The book is divided into two parts—the nature of biological research and the bases of biological thinking. In its broadest and most general terms, a biologist wants to know and above all to understand form, structure, and behavior of living things; the chemical and physical factors in their functioning; their development, reproduction, and genetics; their relation to the nonliving environment and to one another; and their history. To do this he needs facts which may be there already or which may have to be gathered. Then he must observe, experiment, and organize the facts. Next, he must interpret the marshaled evidence. Next he must seek to validate or invalidate his solution. These four internal or personal processes lead to the fifth, which is to tell his fellow investigators, his fellow students, and the world at large what he has found out. In short, to write, illustrate, and teach. For those who have succeeded in getting this far, there is a sixth goal. This is to fit his information, his ideas, and his hypotheses into the proper context of general thought; to criticize the presuppositions and methods of attack, and to discover how all these elements are interconnected. These urges and their realization become in effect the theme of this book.

First of all, one chooses a problem, descriptive or theoretical. Often the proper choice hinges on skill at rejection. Then one is confronted by the problem of inspiration and discovery. One moves from phenomena to theoretical interpretation. Progress may be made by the use of logic and by analogy used but not overused, always trying to avoid the rigidity which comes from overgeneralization. And eventually one reaches the time and need for exposition. Here not only the direction but the method of travel varies, since discovery comes somehow out of the mass of associations. Ultimately, perhaps after a great many conscious and unconscious trials and errors, inspiration fashions related things into a new pattern. Thus what may have been fairly nebulous in the original work has got to be put into a coherent form in thought, and thought must use the only symbols it has, namely, words. The achievement but not the matter of writing is described by Arber as follows: "If the thought is shaped with delicate economy, and has become strong, clear-cut and supple, and if the words materialize it with absolute precision, so that matter and manner are indissolubly fused, the elusive quality called style is won without wooing; but this recipe is as difficult to follow as it is easy to enunciate."

Speaking, reading, or writing are linear one-at-a-time processes. Twist, turn, curl about as they may, they can deal with but one fraction of one concept at a time. Sequence and emphasis, fatigue and concentration, all are important in the transmittal of ideas. The exquisite complexity of this molding ideas into language is illustrated by Arber as follows: "The biological explanation of a phenomenon is the discovery of its own intrinsic place in a nexus of relations, extending indefinitely in all directions. To explain it is to see it simultaneously in its full individuality (as a whole in itself), and in its subordinate position (as one element in a larger whole). On such a definition, classification is treated as one of the corollaries of explanation."

In the second half of the book, the bases for biological thinking, the sixth stage is reached, that of contemplation. It focuses and becomes fused on the conception of truth,

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

which is the target not only of biological thought but of all philosophic thought. In short, one again comes upon the matter of words, the definitions, the significance, and the meanings of our perceptions. Not only in biology but in many other fields the simplicity postulate is a necessary and convenient instrument, seeking from the multifariousness of reality something with which the human mind can deal. It must be forever vigilant, lest in the process of selection and the urge toward tidiness reality is simplified by consigning all troublesome ideas to the wastebasket. Thus often the baby of biological reality is thrown out with the bathwater in an attempt to reduce the infinitely variable complexity of living things to a state in which we can deal with them.

One of the clearest results of this closely thought out series of essays is the realization that biological antipathies belong not in the "either-or" category but the "both-and" classification. To all who teach, to all who do research, and, in fact, to all who as physicians are inhabitants of the general land of biology, the wise and meaty ideas expressed in this little volume would repay careful study which could be repeated many times to good purpose. Here we have compacted in small compass the distilled and recrystallized ideas of one who has served biology as a devoted servant and who has achieved with distinction the sixth objective—fitting personal endeavors in research into a broad pattern of experiences of human life as we perceive them. I know nothing of Agnes Arber's contributions to morphology in her chosen field, though from this book I suspect that they are distinguished. This small book is the elegant embodiment of the thoughtful career of a biological scientist whose impulse to curiosity has driven her far beyond the externals of morphology of plants into the higher meanings of biology and man as the center of the theme. Teachers and investigators in the realm of medicine would do well to study this collection of ideas with the hope that some would assay such a synthesis for medicine, which suffers from a multiplicity of analyses and poverty of any synthesis at all.

WILLIAM B. BEAN, M.D.

Physician's Handbook. Tenth edition. By Marcus A. Krupp, Norman J. Sweet, Ernest Jawetz, and Charles D. Armstrong. Price, $3. Pp. 500. Lange Medical Publications, Los Altos, Calif., 1958.

With facts accumulating at an exponential rate in medicine, no physician can keep at his fingertips all the information he must have at his fingertips. At least he can't keep it in his head. Therefore, such repositories of data as the "Physician's Handbook" are of great assistance to the physician in practice and to the teacher as well. In the scope of five hundred pages or so, between a skimpy table of contents and a fair index, is packed a world of material essential for the care of patients and the day-by-day life of diagnosis and therapy of modern practice. Useful new procedures are included, as well as those which have withstood the test of time. This book which will fit into a coat pocket is an excellent reference and guide for those practicing medicine or learning it.

WILLIAM B. BEAN, M.D.

Roentgenology of the Chest. By Coleman B. Rabin, M.D., F.C.C.P., and 50 contributing authors. Price, $19.50. Pp. 484, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

In the study of patients with disease of the lungs, a roentgenogram of the chest is nearly always obtained. This is because the chest roentgenogram generally provides valuable information which helps the doctor in making a diagnosis. Chest roentgenograms are generally available even in the smallest hospitals and in fact in the offices of many physicians. In spite of its great utility, the chest roentgenogram does not provide an exact etiologic diagnosis. For example, the characteristic picture of tuberculosis can be mimicked by other diseases, such as upper-lobe bronchiectasis. Then, too, it should be emphasized that if the chest roentgenogram is normal, lung disease is not excluded. The roentgenogram of the chest does not even tell us whether the patient was dead or alive when it was taken. It is a favorite trick of Dr. Julius Comroe to start a lecture with an essentially normal-appearing chest roentgenogram and to announce that this roentgenogram was obtained from a cadaver. However, it does provide extremely valuable information. Since it records only the various densities of the tissues of the thorax to their penetration by roentgen rays, it is amazing that many diseases produce characteristic lesions which, if not diagnostic, at least are strongly suggestive of a specific disease. A good book on roentgenology of the chest is an excellent addition to the physician's library.

This book, sponsored by the American College of Chest Physicians, is a beautiful volume which is well written and magnificently illustrated. The editor has employed a combination of roentgenologists and physicians as contributors to the various chapters. The first six chapters deal with a discussion of the possibilities and limitations of x-ray diagnosis, normal roentgen anatomy, and various special methods, such as mass florography, sectional radiography, and bronchography. The next twenty-four chapters deal primarily with lung disease, although there is a chapter on each of the following subjects: diseases of the chest wall, mediastinal tumors, diseases of the pleura, and diseases of the diaphragm. There is an outstanding chapter on some special signs in chest roentgenology, which includes a discussion of the silhouette sign, the air bronchogram, the vanishing tumor, the butterfly shadow, the sail sign, the egg shell calcification, and many others. There is a valuable chapter entitled "Isolated Nodular Shadows," which contains a discussion of how to make an etiologic diagnosis in the patient with a "coin" lesion. The indications for exploration and for observation of such a patient are enumerated. The chapter on diseases characterized by diffuse interstitial fibrosis is excellent. It includes a discussion of collagen diseases, histiocytoses, neurocutaneous diseases, pulmonary fibrosis, idiopathic pulmonary hemosiderosis, and the Hamman-Rich syndrome (diffuse fibrosing interstitial pneumonitis).

The final portion of the book is devoted to consideration of the heart. This part of the book is good, but I thought it was less comprehensive than the part on lung disease. The first three chapters are devoted to the normal heart, kymography of the heart and great vessels, and angiocardiopneumography. The next three chapters include a discussion of acyanotic forms of congenital heart disease, cyanotic types of congenital malformations of the heart, and acquired diseases of the heart. The last three chapters deal with the pericardium, diseases of the pulmonary arteries and veins, and roentgenology of the aorta.

A book of this type should be profusely and carefully illustrated. This book passes this test with flying colors. The quality of the illustrations is superb. Many occupy a full page in size and approach the size of a regular chest roentgenogram. Each chapter should be followed by an adequate bibliography. Many chapters are followed by an outstanding bibliography, but a few have none. Many of the contributors have supplemented the roentgenographic illustrations with simple well-labeled drawings, which greatly aid the reader. Writing this review from the standpoint of an internist interested in chest disease, I find this to be an excellent book.

GEORGE N. BEDELL, M.D.

The Year Book of Pathology and Clinical Pathology (1957-1958 Year Book Series). Edited by William B. Wartman, B.S., M.D. Price, $8. Pp. 478, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

"The Year Book of Pathology and Clinical Pathology," edited by William B. Wartman, continues to be one of the outstanding books in this series because he manages to add so much personal and individual flavor to what might seem offhand a rather dry and dreary topic for an internist. This particular book is notable for his interesting description of a quinquennial brain-dusting tour of England and the Continent, his extracts from the Widdicombe file, which adorns the pages of *The Lancet* from time to time, a dash of Gilbert and Sullivan, and other items, which make the book a pleasure to read through. This, of course, is a bonus in addition to the wide variety of articles abstracted and the reproductions of many effective photographs and illustrations. Without such books as these, the busy physician, the busy internist, is likely to get lost hopelessly in the maze and mass of proliferating publications.

WILLIAM B. BEAN, M.D.

Preventive Medicine for the Doctor in His Community: An Epidemiologic Approach. Second edition. By H. R. Leavell, E. G. Clark, and 19 contributors. Price, $10. Pp. 688. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

The first edition of this book was entitled "Textbook of Preventive Medicine" and had as its objective an epidemiologic approach to preventive medicine for those expecting to enter the private practice of medicine or dentistry. It attempted and succeeded in developing a philosophical approach to the subject. The title of the second edition emphasizes this point of view, and its preface reiterates the objectives. There are nineteen contributors, all of whom are competent in their respective fields and present their material with the common goal in mind.

Certain changes in titles and rearrangement of chapters has taken place, and the number of chapters has been increased from eighteen to twenty-one. The book is now divided into three parts, namely, Part I. Basic Principles, Part II. Application of Principles, and Part III. Public Health—Preventive Medicine is Organized Community Action. The first three chapters deal with the "what" of, the levels of, application of, and an epidemiologic approach to preventive medicine, while Chapter 4 deals with biostatistics.

Part 2 begins with a change in title for the first chapter to "The Prevention of Communicable Disease" from "The Prevention of Infectious Diseases." The chapter has been entirely rewritten by new authors and has been much enlarged. There follow in this part chapters on "Nutrition in Preventive Medicine," "Long-Term Illness and the Effect of the Aging Process on Health," "The Prevention of Cancer," "Preventive Factors in Allergy, Accidents, Alcoholism, Diseases of the Sense Organs and Surgical Procedures," "Natural History and Prevention of Oral Disease" (new), "Genetics and Preventive Medicine," "Maternal and Child Health," "Mental Health," "Occupational Health," "Preventive Services in Individual Practice," and "Rehabilitation as a Phase of Preventive Medicine." The term "chronic disease" has given way to "long-term illness."

The third part consists of five chapters on the doctor and his community, and here the remainder of the new chapters are found. A chapter entitled "Health Screening" in the first edition has been deleted in the second edition, and some of the material, incorporated in the chapter on long-term illness in Part II. Although the number of tables in the text remain essentially the same, the number of illustrations has doubled with the addition of charts. Chapter bibliographies and the index are good.

The book is well written and covers the subject in a style which is pleasing and informative for the groups it is proposed to reach. The authors do not intend the book as a reference work or as a text for the teaching of public health administration. It does, however, satisfactorily present the epidemiologic approach to preventive medicine for the benefit of the medical practitioner, whether generalist or specialist, and from the reading of it any medically trained person will have gained a new insight into the problems of preventive medicine and should be better prepared to follow its principles in his community.

FRANKLIN H. TOP, M.D.

College Men at War. By John P. Monks. Price, $10. Pp. 310, with many tables. American Academy of Arts and Sciences, 280 Newton St., Brookline Station, Boston, 1957.

The American Academy of Arts and Sciences has made a handsome volume in publishing the late John P. Monks' painstaking and detailed study of what happened to a small group of college students who had already been selected for a different kind of long-term investigation in the Grant Study at Harvard. When they joined the armed forces in World War II, there was a unique opportunity for using human material, men who before going into their several fighting stations had been studied by the same psychiatric, psychological, physiological, anthropological, and social methods. This provided the base-line data as a standard for comparison. The purpose of the study reported in the book was to find out, if possible, what kind of college men did well at war and why. Were volunteers better than conscripts? What happened to different kinds of people under the frustrating regimentation of a completely unfamiliar military existence? How did different kinds of people fare in combat? What effects did combat have upon them?

When I opened this book I could not help feeling that it was going to be a glorified boondogle altogether unlikely to give a fruitful answer to any of the questions. Thus I took the book up and put it down many times before I finally got into it. Then I found, to my surprise, that it was a study which should be interesting to many people for many reasons. As a physician who saw four years of service in the Army during World War II, I had my own special interests. Furthermore, as an investigator in a small laboratory of applied physiology, I had been in many research enterprises dealing with acclimatization to heat and cold, Atabrine, effects of noise, gun fumes, fatigue, and claustrophobia in tanks, with the opportunity to observe troops in deserts and jungles as well as in laboratory hot rooms, in ration tests, and in combat. Further studies to develop methods to evaluate fitness, preselection, and other problems give me a background of sympathetic concern for the subject of "College Men at War."

The capital conclusion from Monks' observations is that of all the factors which determine success in any military occupation or career, the overriding one is *motivation*. Thus, volunteers

do better than conscripts. Those who see a fruitful employment of their talents do better than those who feel frustrated and sit pouting and twirling their thumbs. In this group of Harvard students, keen motivation was associated with excellent vision, good adjustment, personal pride, high performance level, R. O. T. C. training, a masculine build, interest in the social sciences, being an undergraduate at the time of entering military service, some wealth, and having attended a private school. The successful military man emerged as a highly motivated athletic extrovert with good physique and physical performance, few worries, and only modest academic emphasis. He got overseas and into combat. On the other hand, the military person who was less successful had attended public school; was self-driving, moving up the socioeconomic ladder; was likely to be an imaginative, creative, artistic person, with medium or weak masculine traits, linear build, interest in the physical sciences, inhibited, shy, with poor vision, and no inclination toward sports. He tended to be an enlisted man who thought he was ill-fitted for what he was obliged to do, made poor adjustment, thought his performance was inadequate, had little pride, usually was not in combat or overseas, and endured little or no danger. He was the tense, annoyed, spindly, bespectacled misfit, academically strong but likely to feel and be thought a goof-ball (the Army had a more vivid word for him).

In the group as a whole there had been variation in interest or concern about the war before Pearl Harbor. Most wanted to graduate from college before going to war. Despite some failures, most of the men eventually served in a capacity for which they thought they were fitted. They tended to serve as specialists in specialized capacities. They thought that training in the armed services, except in the field of leadership, was excellent. They were notably intelligent in analyzing their difficulties. They resented the rigid social system in the armed forces. There was universal anxiety in the face of danger but not sufficient to affect combat efficiency adversely. Combat performances generally was very high. Though psychic difficulty was considerable, there was little neuropsychiatric disability. Military service did not impair health except for injuries. The men found the military generally to be unsympathetic toward scientific investigation. It could not be said whether changes in the men resulted from maturity, wartime experiences, or both. Everyone felt more social responsibility in the postwar world. Formal religious affiliation was uncommon, though there was a high acceptance of the "golden rule." The prospect of return to active duty in the Korean War was met with consternation and dismay.

The message of this book should be of prime concern not only to physicians and to businessmen at large but particularly to those concerned with military preparedness. It has been our fate in this democracy that the training, clothing, and feeding of our converted civilians in war tends to be handled in the light of mistakes of the previous war. There had been very little continuity of research in the important minutae of daily life in the armed forces up to World War II. Regardless of what form of scientific destruction may be employed, the lessons recorded in the Grant Study and the experience of many in World War II put great emphasis on the prime importance of learning what we can about motivation, seeing whether it can be fostered—what are its proper origins, not how it can be fabricated from the exigencies of propaganda or the devices of Madison Avenue.

WILLIAM B. BEAN, M.D.

Gestation: Transactions of the Fourth Conference, March 5, 6, 7, 1957. Edited by Claude A. Villee, Ph.D., Assistant Professor of Biological Chemistry, Department of Biological Chemistry, Harvard Medical School, Boston. Price, $4.50. Pp. 216, with 62 illustrations. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1958.

This book represents the transactions of the fourth conference dealing with Gestation. Four subjects are presented: "The Physiology of Fetal Fluids," "The Origin of Amniotic Fluid," "The Morphologic Manifestation of the Uptake of Materials by the Yolk Society of the Pregnant Rabbit," and "The Development of Fetal Immunity."

The method of presentation of material is unique. The essayist does not present a paper but rather highlights, in an informal manner, some of the more interesting aspects of his research. During this presentation there are frequent interruptions by the participants, in the form of questions, criticisms, and comments. The style of publication of the "Transactions" follows directly this method of presentation at the meeting. The "Transactions" will be of limited value, but those interested in the research aspects of this field of reproduction will find the material very interesting and stimulating.

W. C. KEETTEL, M.D.

Problems of Human Pleasure and Behavior. By Michael Balint, M.D., Ph.D., M.S., L.R.C.P., L.R.C.S. Price, $5.95. Pp. 300. Liveright Publishing Corporation, 386 4th Ave., New York 16, 1957.

This is a collection of essays ranging in time of publication from 1923 to 1956 and running the gamut from sex and society, masturbation, the libido, and the dissolution of objective representation in modern art to a series of biographical sketches of individual persons who have influenced the psychoanalytic movement in one way or the other. Perhaps the most perceptive and sympathetic of these, and surprisingly so, is that of Pavlov, since his views are so radically opposed to those of most psychoanalysts. In this book there is even an excursion into extrasensory perception, which seems to have a very close relationship to certain aspects of the psychoanalytic movement. There is relatively little of the jargon of psychoanalysts. Most papers in this book are readily understandable by the average physician, or at least large parts of them are. There are searching inquiries into discipline and punishment and our rather immature conceptions regarding them. The most refreshing aspect of the whole book is the recurring theme, so rare in writings on psychoanalysis and uncommon in its practitioners, of emphasis on the need for research, comparison, control, and objectivity. This is exemplified in the following quotation "Physicists have learned at their own expense that when making any observation whatever, the temperature and the pressure obtained during the observation must be carefully measured and recorded. The reason for this is the empirical fact that there are only very, very few phenomena such as gravitation, which are not influenced by changes of temperature or pressure. This is a fairly new piece of knowledge, perhaps 200-300 years old. We analysts behave as if we knew that the processes we observe are independent of the emotional temperature and pressure of the situation in which they occur. Very likely just the opposite will be the case. That is why I propose to every analytical observation be added a description of the emotional tension—whether excited, very tense, or relaxed, or even calm—and of the emotional temperature—seething with emotions, indifferent, or even icy cold—under which they were made. It is fair to expect that very valuable material will be produced in this way, and that we may be able to find out a great deal about the ways of the various techniques, i. e., about the observer's parallax." Observer's parallax is recognized by all conscientious investigators. None of us is free from a certain amount of body English in research or in teaching. A great tragedy of the doctrine and proprietary attitude of practitioners of psychoanalysis has been that its most vigorous adherents have dealt with it as religion, with Freud ensconced as the diety. Aspirants must go through a long rigidly prescribed novitiate before initiation. There is but one road to nirvana. When outsiders, looking for enlightenment, criticize, they are likely to be attached in huffish attitude as psychotic or at least disingenuous merely because they question the structure of evidence on which the hypotheses rest. Still, the major problem remains that much of the rubric is based on an approach which is essentially anecdotal and subjective. Thus it cannot, of necessity, be definitive. The great insights of Freud need to be viewed and evaluated as objectively as possible, distinguishing among words, ideas, and facts as sharply as their nature permits. Balint's great contribution is to bring psychoanalysis out from behind the enshrouding darkness of a sacred grove where it is worshipped as a mystique and into the light of scientific research where it may be judged. Thus he is mindful of the provisional state of all science and aware of the need for those psychiatric and psychoanalytic insights which can stand the glare of inquiry to permeate more widely through the teachings and practice of medicine.

WILLIAM B. BEAN, M.D.

Gynecologic and Obstetric Pathology. Sixth edition. By Emil Novak, A.B., M.D., D.Sc. (Honorary, Trinity College, Dublin and Tulane) F.A.C.S., F.R.C.O.G., and Edmund R. Novak, A.B., M.D. Price, not given. Pp. 650, with 683 illustrations, 25 in color. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

The sixth edition of Novak's classic book has been changed materially from the 1952 edition. Despite the fact that the senior author died Feb. 3, 1957, and had been in ill health prior to this time, he was able to contribute generously to this edition. In the future this book will be written by his son and Dr. Donald Woodruff.

A new chapter has been added, on gynecologic and obstetric exfoliating cytopathology. This material is clearly presented and fulfills a real need. The chapter on implantation and placentation has been completely rewritten and brought up to date in light of recent medical advances. Other chapters have been modified, and many of the older illustrations have been replaced by newer illustrations. These changes have kept this book up to date.

This textbook has always been considered as the standard reference book of obstetrical and gynecological pathology. The material is presented in an authentic, clear, concise style which is easy to read and understand. The illustrations of both the microscopic and the gross lesions are a valuable feature. There is complete coverage of the entire field of obstetric and gynecologic pathology. In addition to a complete description of the gross and microscopic pathology there is excellent correlation of symptomology and pelvic findings. The endocrinologic aspect of each pathologic entity is also adequately described.

This book will have wide appeal to persons interested in obstetrics and gynecology and also to general physicians and internists interested in this specialty.

W. C. KEETTEL, M.D.

The Student Life. By Richard E. Verney, M.B., F.R.C.P.E., D.R. Price, $3. Pp. 214. E. & S. Livingstone, Ltd., London, distributed by Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2, 1957.

Admirers of William Osler, a select and hardly diminishing band, have made many efforts to keep his memory alive. Camac collected "Counsels and Ideals from the Writings of William Osler," which for a time had a wide distribution. For many years, Mr. Eli Lilly presented a copy of "Aequanimitas" to every graduate of a medical school in the United States. At the time of the Osler centenary, complete numbers of the ARCHIVES, the *British Medical Journal*, the *Bulletin of Johns Hopkins Hospital*, and *Canadian Medical Association Journal* were devoted to Osler. Many new items came to light, particularly from those who in their youth had known him personally. Thus the image of Osler left by Cushing was enlarged and made more commodious. But it is in Osler's writings that we see him best, not in what others say of him. One finds behind the charm and the elegance a melancholy man, one who "laughed that he might not weep."

Shortly after the Osler centenary, I published a collection of aphorisms culled from his writings and from a selection of notes my father made when an undergraduate student at Johns Hopkins in classroom and on ward rounds. This was entitled "Sir William Osler: Aphorisms from his Bedside Teachings and Writings," published by Schuman, in 1950. There have been innumerable reprintings of his essays and several printings of Cushing's "Life of Osler," this being the mirror through which most people of my generation first knew him.

Pratt's "A Year with Osler" gave a first-hand record of Osler as a clinical teacher and an organizer of teaching. Felix Cunha had printed privately an essay entitled "Osler as a Gastroenterologist." In 1951, the Osler Club in London brought out an anthology entitled "Selected Writings of Sir William Osler," and in the same year William White published his address on "Sir William Osler, Historian and Literary Essayist," and W. R. Bett wrote of "Osler: The Man and the Legend." Thus there has been a continuing flow of books and articles as well as innumerable quotations in journals whose editors hate to leave a portion of a page blank.

"The Student Life" is thus the most recent of a long lineage. Verney has been a lifelong admirer of Osler. He has made his compilation by rearranging excerpts from many of his essays and writings, using an arrangement somewhat similar to the one I used in the collection of Osler's aphorisms. He has also seen fit to change some of the phrases and words, substituting the names of the latest mechanical devices of the machine age for terms only slowly becoming anachronistic. Personally, I do not believe that a reference to carriages is improved by changing to motor cars. Many will agree that efforts to modernize the writings of people who have assumed the important position in history rarely lead to improvements. Imagine the results of modernizing Sir Thomas Browne or Aubrey and having them appear in the impeccable guise of twentieth-century prose instead of with the freshness of an archaic style, quaint, charming, a little foxed and dog-eared.

Perhaps Verney's footnotes will help a few persons, though to me they appear incredibly redundant for anyone who would be interested in reading Osler in the first place. There are a few errors. Ether was not discovered in 1846 by Long and Morton. I disagree with the footnote stating that "Religio Medici" is not likely to be the same solace today as it was a couple of generations ago. Every man to his own taste. Perhaps only an old friend would fuss at remodelling the addresses and papers. Those who do not object to finding Osler's essays divided, shuffled, and redealt will not be disturbed by an unlikely postscript of nine pages containing a biographical sketch of Francis Adams, a fascinating and wonderful person, but a rather curious afterthought in such a book as this. So much for carps and crochets. Osler can withstand much patchwork and come out fresh, as encouraging and inspiring as ever. Verney, in his own

way, has brought Osler up again for our contemplation. This is one of the only Osler books with an index, which, despite its skeletal form, is of some help. In this one sees the long hand of William Francis. The main result of reading this book was to get out some of Osler's original essays and read them. Surely this is the most fruitful result of reading it.

WILLIAM B. BEAN, M.D.

Physical and Behavioral Growth. Report of the 26th Ross Pediatric Research Conference. Price, not given. Pp. 101. Ross Laboratories, Columbus 16, Ohio, 1958.

This conference report covers one hundred one pages and contains numerous graphs. The reports of this conference have been abbreviated but are in very clear and understandable form. They cover pediatrics from infancy to adolescence. The participants in this conference are experts in their field and report on not only their own research but also research of other persons. The conference starts out with neurological development during the first year of life and the influence of prenatal and paranatal factors on behavior, as well as maternal anxiety during pregnancy and its effect on fetal behavior.

It then reports on the preschool child and his relationship to abstract thinking, behavior of the preschool child, and parent-child interaction. Physiologic variabilities during childhood are also covered—those having to do with temperature, evaluation of skeletal maturation, and blood pressures. There are also interesting observations on fluctuations in mental test scores and alterations in intelligence quotient in relation to personality variation. This report also brought out very clearly that developmental maturation during infancy is difficult to correlate with intelligence tests done later in life in the normal child.

Thirty pages are used to cover the adolescent. There is a chapter on competitive athletics and physical fitness—the difference in maturation in boys and girls. The emotional patterns of adolescents and the philosophy of growth are also covered. This is a small booklet covering a large amount of pertinent information as to the physical growth and development of infants and adolescents.

JOHN A. BIGLER, M.D.

The Year Book of Drug Therapy (1957-1958 Year Book Series). Edited by Harry Beckman, M.D. Price, $7.50. Pp. 518, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

If one did nothing else except read the brief introduction of Beckman, voicing his despair at the growing trend of launching drugs for use by the unwary public without tests or with inadequate tests, he would be well paid for looking into this book. Much space is given to evaluation of tranquilizers and stimulants, to cardiovascular diseases, and to infectious disease, and there is relatively little dealing with the liver, neoplasm, vitamins, and the thyroid. For the most part there have been relatively many fewer new compounds launched in these areas. Without the help of "The Year Book of Drug Therapy," it would have been difficult to keep up with therapy in the very wide variety of diseases an internist or a general practitioner may encounter in his work. Whether Modell's "Drugs of Choice" will provide too strong competition for this member of the Year Book Series remains to be seen.

WILLIAM B. BEAN, M.D.

The Year Book of Endocrinology (1957-1958 Year Book Series). Edited by Gilbert S. Gordan, M.D., Ph.D., F.A.C.P. Price, $7.50. Pp. 381, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

The field of endocrinology has come a long way in the last decade. Indeed, the whole science has developed almost within the memory of many people still contributing to the field. This activity is reflected in this culling and condensation of medical reports. If they reflect justly the volume or direction of interest one would say that endocrine influences on neoplastic disease is least. This is followed by the parathyroid, then the hypophysis and the hypothalamic area. Next come the reproductive system, carbohydrate metabolism emphasizing the oral hypoglycemic agents, the adrenal gland, and, finally, most space is given to the thyroid. There is much to relate about steroid chemistry, with the new synthetic materials getting a lot of attention. Thyroiditis, at least some varieties, appears to be falling into the category of disorders in immune and autoimmune mechanisms. One can find a good review of the rather startling developments which followed Murray Barr's demonstration that chromatin sex patterns can be identified readily in smears from the mouth or vagina. More and more we are realizing

that sex is a relative thing. Our immutable standards for masculinity and feminity have received a rude shock, for it now seems reasonably certain that lack of sexual development in young "girls" once though to have undeveloped ovaries usually results from intrauterine damage or atrophy of the testes in genetic males and that at least some infertile "men" with gynecomastia and atrophic testes (Klinefelter's syndrome) have the genetic chromatin pattern of females. No wonder some men are sterile, if they are not men after all. Thus again science is demonstrating that things are rarely what they seem. This material and much more is all marshalled before us in Gordan's book.

WILLIAM B. BEAN, M.D.

Memories and Reveries. By Frederick E. Jackson, M.D. Price, $3. Pp. 153. Exposition Press, Inc., 386 4th Ave., New York 16, 1958.

I can learn something from reading any thoughtful medical biography or autobiography. Though I opened this book with misgivings lest it be another potpourri of whimsical nostalgic reflections, I found it to be the friendly chatty miscellaneous reveries and memories of a boy who grew up in the country, became a physician, retired, and the while reflected of life and people. He had been given to this habit of reflection all his life. Thus he has many pertinent things to say about patients, people, growing up on a farm, and the kind of a boyhood some of us remember, one which is becoming extinct in our society. I assume that the observations set forward are truthful. They have the natural flavor of a candid and guileless person. The book is written well enough, despite the protestations of its author. It is unusual in a book written in the afterglow of a medical career to find the frank admission that medicine had never been the real profession of choice. Instead, Dr. Jackson was a frustrated author, though I think he should be pleased with the book he has produced in his old age. Everyone has thoughts on the theme "it might have been." But Dr. Jackson does not make any effort to be a cracker-barrel or drugstore philosopher. For those who are interested in the unpretentious but straighforward views of a retired physician with a thoughtful turn of mind, this book is recommended. Not deep, but cool and clear.

WILLIAM B. BEAN, M.D.

Manual for Nutrition Surveys. Compiled by Interdepartmental Committee on Nutrition for National Defense. Price, $1.50. Pp. 160, with illustrations. Superintendent of Documents, Government Printing Office, Washington 25, D. C., 1957.

Proceedings of New England Conference on Human Nutrition. Sponsored by Florida Citrus Commission, March 22-23, 1956. Price, not given. Pp. 90.

Food Acceptance Testing Methodology. Edited by David R. Peryam, Francis J. Pilgrim, and Martin S. Peterson. Price, not given. Pp. 115. National Academy of Sciences, National Research Council, 1954.

Dietary Prevention and Treatment of Heart Disease. By John W. Gofman, M.D.; Alex V. Nichols, Ph.D., and E. Virginia Dobbin. Price, $3.95. Pp. 256, with illustrations. G. P. Putnam's Sons, Inc., 210 Madison Ave., New York 16, 1958.

Nutrition, food production, dietetics, and just simple eating occupy a large and often pleasant part of human existence. They are vital in the evolution and survival of mankind, both collectively in nations and races and individually in the life of a single person. The processes and emotional concern over intake and output have inspired some remarkable doctrines in psychiatry. Nevertheless, the field of nutrition has been one of the most poorly cultivated of all areas of clinical investigation. For every person working intensively on problems of clinical nutrition, there are at least one hundred and maybe five hundred working in cardiology. By a curious quirk of fate, the lines of attack are now converging. Suddenly it becomes necessary for a cardiologist to know a good deal about nutrition and metabolism, as the changing philosophies about arteriosclerosis are veering away from stress and focussing on calories, cholesterol, and fats. These four books approach nutritional problems from widely separate vantage points, in many respects hardly comparable. The "Manual for Nutrition Surveys" is a document which epitomizes much of the large experience gained during World War II and thereafter in ration surveys, nutrition surveys, and a consideration of the ecology of man, with emphasis on nutrition. If this book could be employed universally as a guide for nutrition surveys, we could compare results of such studies the world over. Unfortunately the most reproducible aspects of such surveys, the biochemical studies, are ordinarily the least valuable.

Clinical observation, depending as it does on training, experience, and individual bias, introduces a substantial subjective element which can never be surmounted unless one person or one group conducts all the tests. Even here one finds some day-to-day variation. As a distillate of a vast body of experience and skill, this outline for conducting nutrition surveys and for evaluating the nutritional state of an individual person or a group is an excellent guide. Adopted universally it would give better grounds for drawing comparisons about nutritional states over all the world than we have ever had.

"Food Acceptance Testing Methodology," despite its grotesque title, is a good report of a symposium sponsored by the Quartermaster Food Container Institute and the Quartermaster Research and Development Command of the U. S. Army Quartermaster Corps. It is published under the auspices of the Committee on Foods of the National Academy of Sciences of the National Research Council. I am forcibly reminded of the remarkable confusion in World War II, where the program for packaged emergency rations almost wound up in disaster because of the strong concern authorities then had for making a ration in which, for each day and preferably for each meal, there was a liberal allowance of vitamins. But in order to meet the specifications of weight, shape, keeping qualities, packaging, and so forth, it became necessary to use liver extract, yeast, and soy bean concentrates in the needed food. The result was that food items with exotic tastes, perfectly satisfactory as an hors d'oeuvre for a taste panel, had such high satiety value that the ration soon became useless. Since the responsibility of the quartermaster in the field was to get one ration per day to each man, and since emergency K and C rations were easy to handle, combat troops frequently found themselves using rations for purposes other than those for which they had been designed. Fifteen years ago, I was assigned the job of writing a critique of these rations. The main points I made were these: Acceptability of a ration is the first requisite. Vitamins are not important over the short haul. A taste panel is a poor guide to judge acceptability in combat. I recommended that field trials should be held before procuring or selecting rations and that recommendations and changes should be evaluated in or near combat. It may amaze some veterans of World War II whose memories of K and C rations are those of nostalgic nausea to learn that after a large-scale ration test, changes were introduced. Common foods and more variety in the improved rations increased their acceptability. They were used by troops in combat in the Pacific Theater for as long as five months, with excellent health, morale, and fitness and no more than the usual quota of gripes. The story of the later validation of changes in rations and a review of tropical deterioration and nutrition combined with companion data obtained by another nutrition team in Burma and India were published in *Medicine*. The myth of a specific tropical deterioration or special tropical food requirement was exploded.

Now, after this parenthesis, the main feature of the manual on food acceptance technique is an extension of such studies. It seems to subscribe to the thesis that it is now feasible to obtain good preliminary screening by a taste panel. The overriding importance remains, however, of testing combat rations first in a field test and later as nearly under the circumstances of actual use as possible. But as a manual for screening things suitable for taste panel technique, it is excellent. It is hoped that all the lessons relearned about feeding troops in combat are not fading once more from the memory of man.

"Proceedings of the New England Conference on Human Nutrition" might have been called essays in ecology. Many aspects of the remarkably complex interrelationships of health, disease, and nutrition are considered. There is emphasis on the paradox that with ample foods available we still have food imbalances and deficiencies. There is a proper skepticism about the employment of vitamins as medicines rather than as emergency therapeutic measures for temporary repair. Overweight, underweight, and the role of numerous diseases in undermining nutrition and dental health are discussed in detail. One of the most interesting sections is Dr. Montagu's speech on "Nature, Nurture, and Nutrition," viewed from his broad background of anthropology. "Non-maternal" members of the family is printed "non-material," a misprint not without its point. Harris emphasizes the fallacy of dietary surveys in measuring the amounts of food eaten and the fallacy of believing that economic or even educational status necessarily means a wise selection of food, since it was found that the poorest fed subject was a college president. This brings up all kinds of interesting ideas.

"Dietary Prevention and Treatment of Heart Disease" is the misleading and partly paradoxical title of a book which unfortunately shares the same faults. Riding a single hobby, the Procrustean stretching and trimming of facts to fit doctrine, the belief that most important facts about any disease can be subsumed under one narrow hypothetical construct, reading into

data interpretations which do not bear the scrutiny of intense criticism, are occupational hazards of systematists in all ages and times. Just as critical investigators are increasingly skeptical about the validity of generalizations which attribute to a single all-inclusive specific process, *stress*, so many of the diseases of our times, so also critical investigators and clinicians believe there is much more to arteriosclerosis, coronary and other, than can be contained in the exclusive philosophy of the Sf lipoproteins. Perhaps this was shown most clearly when the American Heart Association conducted a study on the importance of various lipoprotein materials and concluded that the evidence did not support the contention that such Sf factors were the only cause of atherosclerosis. From this opinion the main dissenter was Gofman. Thus this book on dietetics is based on an uncertain hypothesis which has been dignified as a theory and by some has been looked upon as fact. Nevertheless, the book has much practical value in providing instructions for reducing diets, for low-fat and low-cholesterol diets, the employment of which might very well lead to the desired end. This is not the same as saying that results can be guaranteed or that the thesis has been demonstrated or that we know enough to exclude any one of the many other factors or circumstances which dispose to coronary artery disease or atherosclerosis. The crucial point is that the title begs the question. Things which are unknown or purely speculative are set down in an authoritarian tone which seems to imply that all investigators, differing from the philosophy set forth in this book, are rogues or dunces. They may be dispensed with conveniently and forgotten once and for all. The history of medicine and indeed the history of "science" is littered with the wreckage of many an oversimplified system which held sway, diverted the skeptical, but wrought havoc on the gullible for a time and then was cast aside. The nearly impenetrable complexity of problems of causality in most chronic diseases has been skimped or evaded by those to whom a single process or mechanism has its ancient and powerful appeal. The strong effort of the mind required to separate fact from cherished belief is out of the range of many brilliant investigators. Conviction does not change reality. There will be little harm done, since the effects of diet are not controlled by our beliefs about how they occur. After all, there may be some protective folk wisdom in the inveterate resistance with which most patients meet our strongest efforts to make them diet.

WILLIAM B. BEAN, M.D.

Correction

In the article, "Hodgkin's Disease and Pregnancy" by Major Robert B. W. Smith, Capt. Thomas W. Sheehy, and Capt. Harvey Rothberg, in the November, 1958, issue of the ARCHIVES, credit to the Department of Hematology, Walter Reed Army Institute of Research was inadvertently omitted.

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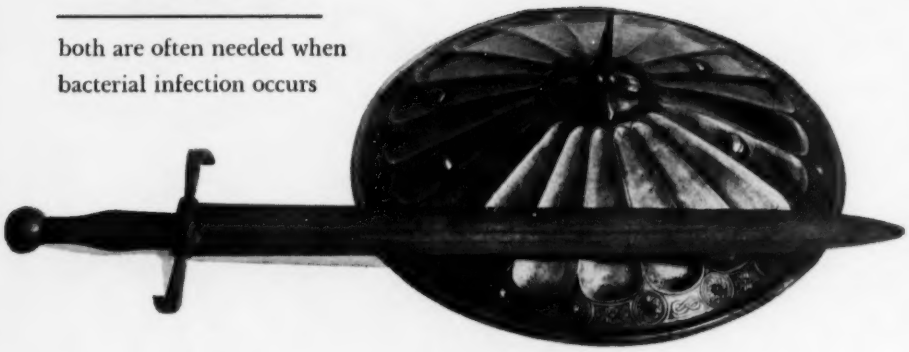

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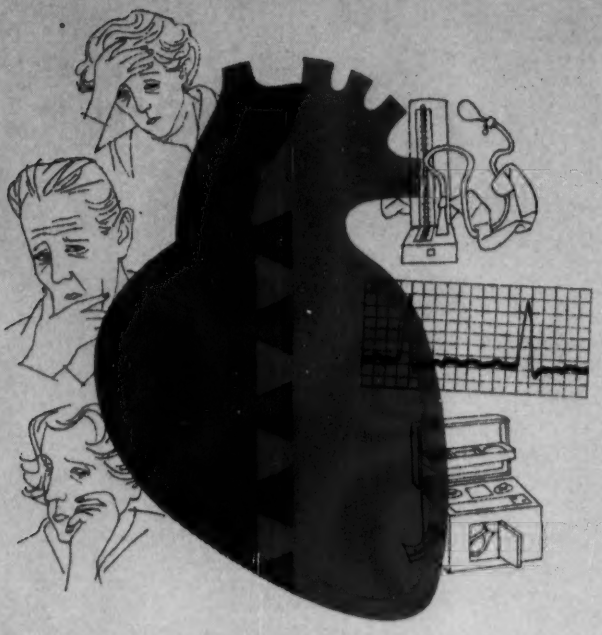

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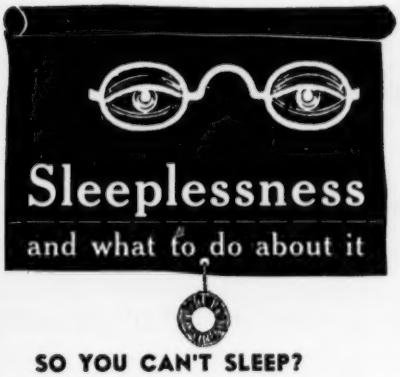

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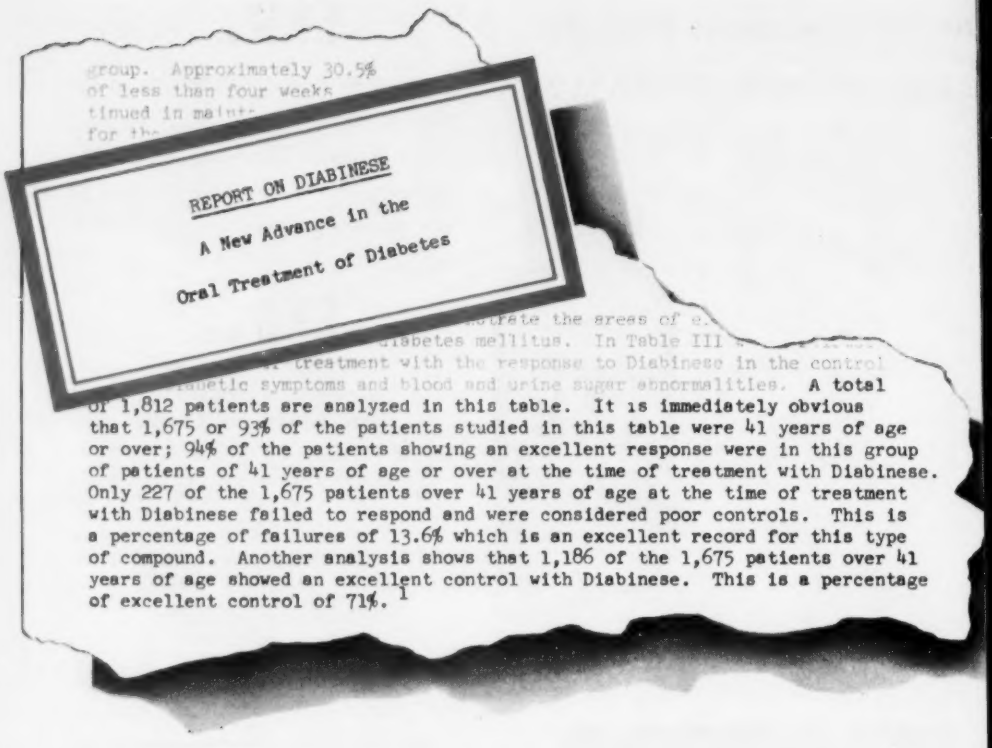
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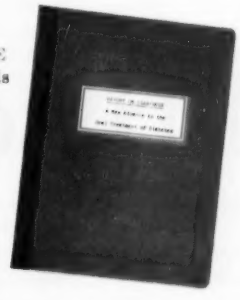

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